CHOLESCINTIGRAPHY AFTER ENDOSCOPIC PAPILLOTOMY
IN PATIENTS WITH AN INTACT GALLBLADDER

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Cholescintigraphy After Endoscopic Papillotomy

in Patients with an Intact Gallbladder

A Thesis Submitted to the

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in Partial Fulfillment of the Requirements

for the Degree of

Doctor of Medicine

by

Michael Alan Price

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This thesis is dedicated to my parents, Morris and Shirley Price, my sister Debra, and my brother David.

This thesis is dedicated to my parents, Marcia and
Shirley Price, my sister Deanne, and my brother Barns

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ABSTRACT

CHOLESCINTIGRAPHY AFTER ENDOSCOPIC PAPILLOTOMY IN PATIENTS WITH AN INTACT GALLBLADDER. Michael A. Price, Michael C. Bennick, Adrian Reuben, John Dobbins, and Morton I. Burrell. Departments of Diagnostic Radiology and Internal Medicine, Section of Gastroenterology, Yale University School of Medicine, New Haven, CT.

The aim of this study was to determine baseline cholescintigraphic findings in persons with an intact gallbladder and an ablated sphincter of Oddi. This information allows assessment of: 1) the reliability of cholescintigraphy for diagnosing acute cholecystitis in this population, and 2) the contribution of the sphincter of Oddi to the physiological process of gallbladder filling in humans. Five subjects with an intact gallbladder, who had previously undergone endoscopic papillotomy, were studied according to the following protocol: 1) Quantitative cholescintigraphy was performed with ^{99m}Tc-DISIDA (5 mCi). 2) Evidence of a patent papillotomy was sought, using ultrasonography and plain abdominal radiography for detection of biliary air, and barium swallow for detection of duodenal-biliary reflux of contrast. Biliary air was demonstrated by plain film in two subjects (40%) and by sonography in one of these two subjects (20%). Barium reflux

occurred only in the two subjects (40%) who had evidence of biliary air on plain film. The gallbladder was seen by cholescintigraphy in three (60%) of the five subjects, including one of the two subjects (50%) with supportive evidence of a patent papillotomy. Additional data are necessary before conclusions can be drawn, but our preliminary results suggest that: 1) Visualization of the gallbladder by cholescintigraphy may occur in a patient following endoscopic papillotomy. In such patients, the reliability of cholescintigraphy for diagnosing cystic duct obstruction (radiologic confirmation of clinically suspected acute cholecystitis) cannot yet be determined. 2) Gallbladder filling can occur even in the setting of a non-functional sphincter of Oddi. Thus, gallbladder filling probably depends upon other physiologic mechanisms, in addition to any role played by sphincter contraction.

NOTE: An additional subject participated in the study after this abstract was submitted for publication. The thesis includes the data from all six subjects.

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INTRODUCTION

This investigation was performed in order to determine baseline cholescintigraphic findings in persons with an intact gallbladder and an ablated sphincter of Oddi. The goals of this study were: 1) to ascertain whether cholescintigraphy is likely to be a reliable test for acute cholecystitis in this population (as it is in patients with an intact sphincter of Oddi), and 2) to elucidate the role of the sphincter of Oddi in the process of gallbladder filling in humans.

Cholescintigraphy employs radiolabelled iminodiacetic acid (IDA) compounds to provide both an assessment of hepatic uptake and excretory function, and a visual demonstration of hepatobiliary anatomy. This test is often used as the primary diagnostic procedure in suspected cases of acute cholecystitis (in patients with an otherwise intact biliary tree). The efficacy of this test has not been evaluated, however, in patients who have undergone endoscopic papillotomy. This is a procedure in which the sphincter of Oddi is severed, usually to facilitate removal of gallstones obstructing the common bile duct.

A second facet of this study was to examine the mechanism by which the human gallbladder fills, as the contribution of the sphincter of Oddi to this process is still unresolved. One theory proposes that the gallbladder fills during the relaxation phase after contraction, as a result

of a pressure gradient from the common duct. An alternative viewpoint holds that filling depends upon occlusion of the terminal common bile duct by the sphincter of Oddi (and/or possibly the duodenal musculature), thereby forcing bile to flow into the gallbladder. If this latter theory is correct, the loss of sphincter contractility after papillotomy would allow bile to flow preferentially into the duodenum instead of the gallbladder. Impaired filling would thus cause non-visualization of the gallbladder by cholescintigraphy, giving a false positive test for cystic duct obstruction.

The Human Biliary System: Basic Structure and Function:

The biliary system consists of the gallbladder and bile ducts. The gallbladder is a small sac which stores and concentrates bile synthesized and secreted by the liver. Ducts connect the liver, gallbladder, and duodenum, allowing movement of bile between these organs. Bile is an aqueous solution of electrolytes, organic anions, bile acids, lipids, proteins, and products of hepatic metabolism, which fulfills both excretory and digestive functions. Cholesterol and metabolites of endogenous and exogenous substances are eliminated in the bile. Bile acids aid in the intestinal absorption of dietary lipids by solubilizing products of digestion in mixed micelles that are readily carried to the mucosal surface of enterocytes.[1-3]

Bile is secreted from hepatocytes into microscopic channels known as bile canaliculi. These structures coalesce to form successively larger tubules (bile ductules and intrahepatic bile ducts) that eventually emerge from the liver as the right and left hepatic ducts. These converge to form the common hepatic duct, to which the cystic duct joins the gallbladder to the biliary tract. The mucosa of the proximal cystic duct is arranged into crescentic folds known as the spiral valves of Heister, which may participate in the regulation of bile flow into and out of the gallbladder. The common bile duct arises from the union of the cystic and common hepatic ducts. It courses through the duodenal musculature, and opens into the duodenum at the papilla of Vater. The main pancreatic duct joins the common bile duct at the ampulla of Vater (in the most common anatomic configuration), to form a single orifice at the papilla. The terminal common duct and ampulla are encircled by the sphincter of Oddi, a band of muscle tissue anatomically and embryologically distinct from the duodenal musculature.[3-6] Figure 1 depicts the anatomy of the human biliary tract.

Bile enters the gut mainly in response to the presence of fat in the duodenum. This stimulus triggers the secretion of the hormone cholecystokinin (CCK) from intestinal mucosal cells. CCK is the primary mediator of post-prandial biliary motility; its action induces contraction of the gallbladder and relaxation of the sphincter of Oddi, which results in the delivery of stored bile into the gut.[1,3,4] Autonomic
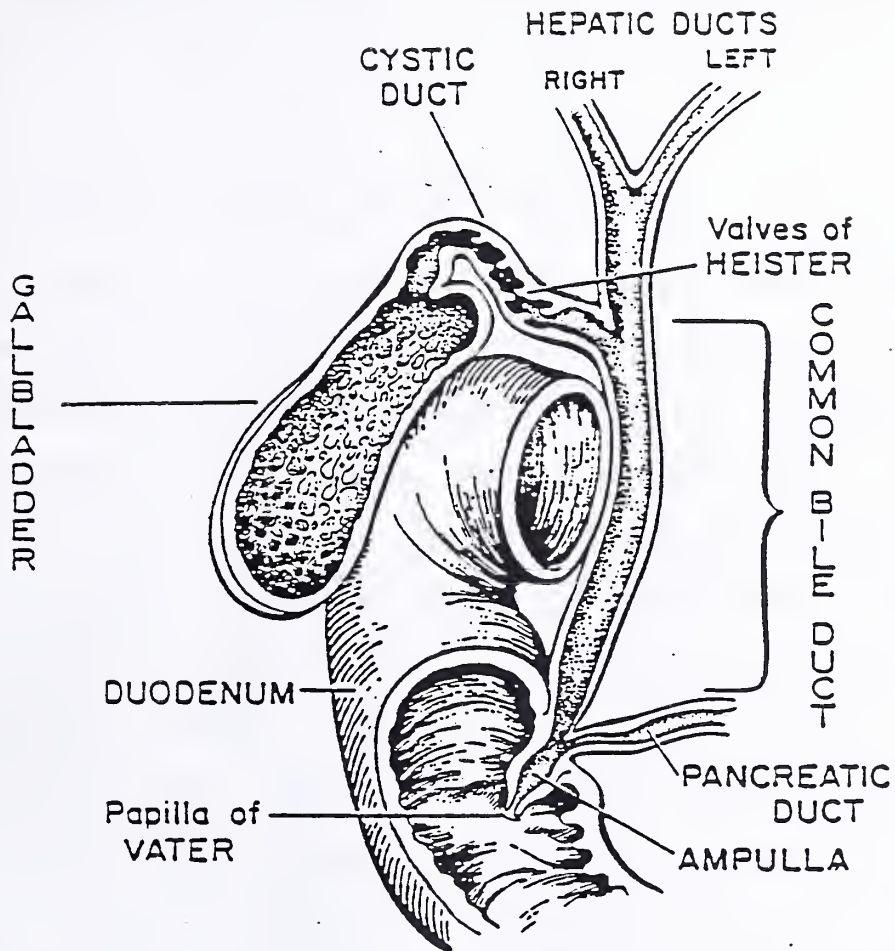
Figure 1: Anatomy of the human biliary system (modified from Hogan, Dodds, and Geenen, 1983).[4]

pathways, additional gut hormones (including motilin, secretin, pancreatic polypeptide, vasoactive intestinal polypeptide, and glucagon), enkephalins, and prostaglandins also influence biliary motility, although their precise physiologic roles have not been fully characterized.[3,4]

The Pathophysiology of Gallstone Disease:

Gallstones are solid concretions which form when substances such as cholesterol, bilirubin, calcium, and proteins precipitate out of solution in bile. Stones usually form within the gallbladder, but also develop in the bile ducts in rare instances. Gallstones are quite prevalent in Western countries, occurring in about 10-20% of adults in the United States. Three major types of gallstones exist: cholesterol stones, mixed stones, and pigment stones. Cholesterol and mixed stones, which consist primarily of cholesterol, are common in Western populations. Pigment stones, composed mainly of calcium bilirubinate, are more prevalent in Asian countries. The exact pathogenesis of gallstones is not entirely clear, and probably depends upon multiple factors. Supersaturation of bile with cholesterol is a prerequisite for cholesterol stone formation. Risk factors associated with the development of cholesterol gall-stones include: 1) advanced age, 2) female sex, 3) obesity, 4) use of certain drugs (clofibrate, thiazide diuretics, and estrogens), and 5) certain diseases (e.g., ileal disorders,

cystic fibrosis, diabetes mellitus, and hyperlipidemia).
Conditions which may predispose to the development of
pigment stones include alcoholic cirrhosis, biliary infec-
tions, and chronic hemolysis. Genetic and dietary factors
may also play a role in gallstone pathogenesis.[3,7-9]

Gallstones may remain clinically silent for years. A
study of 123 asymptomatic persons with gallstones detected
by screening found only an 18% probability of developing
resultant biliary symptoms or complications over a 20 year
period.[10] However, cholelithiasis can lead to a variety of
illnesses. Intermittent obstruction of the cystic duct by a
stone can cause episodes of biliary colic, typically
manifested by right upper quadrant abdominal pain. Over
time, stones in the gallbladder may cause chronic chole-
cystitis, a condition characterized by chronic inflammatory
changes in the gallbladder wall. Impaction of a stone in the
cystic duct is the most common cause of acute cholecystitis,
an acute inflammation of the gallbladder which usually
necessitates cholecystectomy. Stones may also lodge in the
bile ducts (choledocholithiasis) with resultant obstruction,
possibly leading to ascending cholangitis and/or pancrea-
titis. These conditions can be life-threatening, and may
require interventional therapeutic measures to relieve the
obstruction. Gallstones are also associated with the
development of carcinoma of the gallbladder.[3,8,9]

Surgical Management of Biliary Obstruction:

Until the 1970's, surgery was the only interventional form of therapy available for biliary obstruction. Operative procedures for relieving common duct obstruction include 1) lateral choledochotomy (common bile duct exploration) and choledocholithotomy,[11] 2) sphincter ablation by transduodenal sphincterotomy or sphincteroplasty,[12] and 3) biliary bypass techniques such as choledocho- and cholecystoenterostomy.[13] Patients with an *in situ* gallbladder presenting with choledocholithiasis usually undergo combined cholecystectomy and common bile duct exploration.

The risks of biliary surgery are minimal in young and healthy patients. A large American surgical series of 11,808 patients reported a 0.1% mortality for cholecystectomy among patients younger than 50 years operated on for chronic cholecystitis, and a 0.9% mortality for similar patients undergoing cholecystectomy with common duct exploration.[14] A recent international survey reported overall mortality rates (among all age groups) of 0.6% for cholecystectomy alone and 4.4% for cholecystectomy with common duct exploration.[15] Reported mortality rates for all age groups undergoing surgical sphincterotomy vary from 0-13%, with a mean of 4.6% (total 1061 cases), and those for choledochoduodenostomy range from 0-8%, with a mean of 3.0% (total 733 cases).[16]

Peri-operative morbidity and mortality rise dramatically, however, among patients with advanced age and/or

coexisting illnesses, and in cases requiring emergency surgery.[17-22] For various biliary procedures, surgical mortality rates of 4.0-16.2% have been reported in patients over the age of 60.[18-21] One study noted a 28.6% mortality rate for combined cholecystectomy and common bile duct exploration in patients aged 70 and over.[23] An analysis of several series on elderly patients quoted average mortality rates of 4.4% for elective biliary surgery, as compared to 16.7% for similar operations performed emergently.[22] Studies correlating surgical mortality with specific risk parameters (including age, underlying malignancy, anemia, malnutrition, diabetes mellitus, impaired renal function, hyperbilirubinemia, elevated alkaline phosphatase, and leukocytosis) have shown a tremendous increase in mortality as the number of risk factors increases.[20,21] Thus, while biliary tract surgery is quite safe in younger patients in relatively good health, operative intervention becomes hazardous in elderly persons with complicating illnesses, especially in situations necessitating emergency surgery.

Endoscopic Papillotomy:

In 1974, Classen and Demling[24] in Germany and Kawai *et al.*[25] in Japan independently introduced the technique of endoscopic papillotomy (also called endoscopic sphincterotomy) for the treatment of common duct stones. As an alternative to surgery, this modality has proven safe and

effective in patients posing a high operative risk. Endo-
scopic papillotomy is a therapeutic extension of endoscopic
retrograde cholangiopancreatography (ERCP), an invasive
method of imaging the biliary tree and pancreatic duct.
Using a fiberoptic endoscope introduced orally to directly
view the papilla of Vater, the endoscopist cannulates the
orifice with a catheter passed through a channel in the
endoscope, and injects radiographic contrast material. The
resultant cholangiogram outlines biliary anatomy and demon-
strates the presence of stones or other pathology (see
Figures 6, 12, 14, 20, 24, & 28). If indicated by findings
on ERCP, section of the sphincter of Oddi can be performed
endoscopically, by use of a papillotome (or sphincterotome).
This instrument consists of a Teflon catheter surrounding a
wire snare, one arm of which extrudes from the catheter
lumen for a short distance near the distal end (see Figure
2). Under tension, the catheter flexes in the form of a bow,
with the wire protruding like a "bowstring". After cannu-
lating the papilla of Vater, positioning the papillotome
within the common bile duct, and tensing the wire, the
endoscopist applies electric current to the wire, creating a
10-20 mm incision, which transects the muscle fibers of the
papillary and common bile duct sphincters.[26-31] Sphincter
function is thus obliterated, producing a potentially
permanent opening from the common bile duct into the
duodenum. Figure 3 is a schematic representation of the
technique of endoscopic papillotomy.

Figure 2: Instruments used for endoscopic papillotomy and gallstone extraction: (from L to R), Zimmon papillotome, Dormia basket catheter, inflated Fogarty balloon catheter.
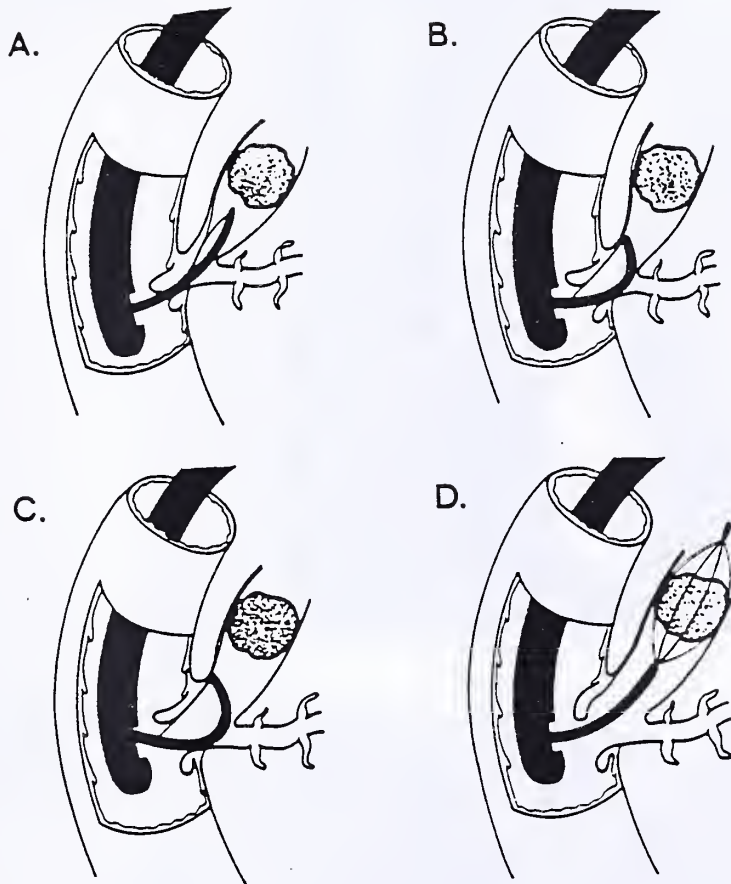
Figure 3: Schematic representation of endoscopic
papillotomy and stone extraction: (A) Papillotome is
inserted into the common bile duct. (B) Tension is applied
to the wire, flexing the catheter and bringing the wire
into position for cutting. (C) Diathermy current is
applied to the wire, incising the sphincter. (D) A stone
is removed with a Dormia basket (modified from Safrany,
1977).[32]

Figure 4: ERCP films demonstrating:

(A) extraction of two stones from the common duct with a Dormia basket (Subject #2).
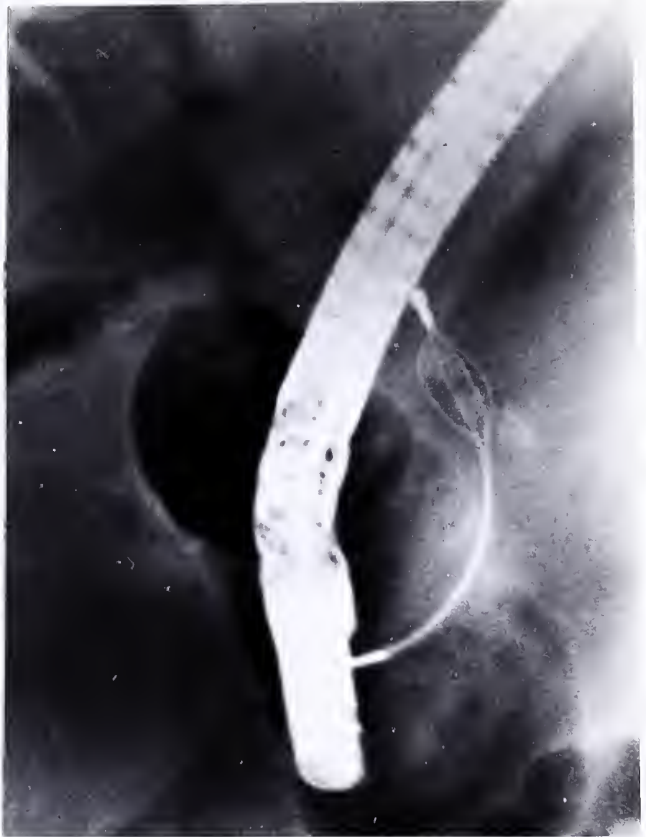
(B) A Fogarty balloon catheter inflated in the common bile duct (Subject #2).

Following papillotomy, endoscopists often allowed ductal stones to pass spontaneously through the enlarged choledochoduodenal orifice, and performed a repeat ERCP to check for clearance of stones from the common duct.[28,32-35] Direct removal of choledochal stones has now become common practice, since this reduces the chance for complications due to retained calculi, and obviates the need for a second endoscopic examination.[31] Instruments employed for stone extraction include: 1) a collapsible wire basket used to capture and retract stones[26,28,31-33,37,38] (see Figures 2 & 4A); and 2) a balloon-tipped catheter used to pull stones out of the duct[31,37,38] (see Figures 2 & 4B). These devices are effective for removing both single and multiple stones. Immediately following extraction, a repeat cholangiogram verifies successful clearance of stones from the duct.

Since its introduction in 1974, endoscopic papillotomy has become widely accepted as an alternative or adjunct to surgery in the management of certain forms of obstructive biliary disease. Choledocholithiasis remains the most common indication for this procedure, accounting for 80-94% of all cases in published series.[28,33-37,39-45] Additionally, this technique has proved successful for: 1) treating biliary obstruction due to benign disorders such as papillary stenosis,[27,28,30,33-37,40-43,45] common bile duct strictures,[35,42] hydatid disease,[35,46] and ascariasis;[40] 2) treatment of chronic pancreatitis[35] and gallstone pancreatitis,[30,41,47-49] and 3) relief of obstructive jaundice

prior to surgery for carcinomas of the ampulla, bile ducts, and pancreas.[27,30,34-37,41-43]

Clinical series from multiple international centers have reported good results with endoscopic papillotomy. Transection of the sphincter of Oddi is achieved in 81-100% of attempted cases[26-30,32-35,39-44,47,50-55] (see Table 1). These figures have improved with increased experience; papillotomy is currently successful in over 90% of cases.[31] Failure to perform the procedure is usually due to 1) an inaccessible papilla in patients with pyloric or duodenal stenosis, juxta-ampullary diverticula, or following Bilroth II gastrectomy or other surgical procedures, 2) technical failure of cannulation, or 3) an uncooperative patient.[28,31,38,56] Successful papillotomy allows clearance of obstructing stones in 85-99% of cases of choledocho-lithiasis.[26-29,32,33,39-43,45,47,50,51,53,55] The overall success rate of endoscopic papillotomy for treatment of common duct stones is thus 76-97%[28,29,31,33,39-44,47,50,55] (see Table 2).

Endoscopic papillotomy is a relatively safe technique when performed by an experienced endoscopist. The reported morbidity resulting from the procedure ranges from 3-20%, with most studies around 7-10%.[27-37,39-45,47,50-55] The most commonly encountered complications include 1) hemorrhage at the incision site, 2) cholangitis (resulting from inadequate biliary drainage, and usually due to impacted stones), 3) pancreatitis, 4) retroperitoneal duodenal perforation, and

Table 1: Reported success rates of attempted endoscopic papillotomy in multiple series.

Investigator(s)	Date	Center	Number Attempted	Number Successful	(%)
Classen & Safrany	1975	Hamburg/Munster	59	50	(84.7%)
Safrany	1977	Munster	265	243	(91.7%)
Koch et al.	1977	Erlangen	267	254	(95.1%)
Safrany	1978	15 Internatl	3853	3618	(93.9%)
Siefert	1978	9 German	955	880	(92.1%)
Reiter	1978	9 German	1499	1403	(93.6%)
Ligoury & Loriga	1978	Paris	155	144	(92.5%)
Montori et al.	1979	8 Italian	239	194	(81.2%)
Nakajima et al.	1979	25 Japanese	485	468	(96.5%)
Cotton	1980	London	134	129	(96.3%)
Geenen et al.	1981	21 U.S.	1250	1113	(89.0%)
Siegel	1981	New York	267	258	(96.6%)
Viceconte et al.	1981	Rome	296	255	(86.1%)
Cotton & Vallon	1981	14 British	679	590	(86.9%)
Mee et al.	1981	London	71	69	(97.2%)
Cotton & Vallon	1982	London	71	70	(98.6%)
Kawai et al.	1983	Kyoto	496	486	(98.0%)
Roberts-Thompson	1984	Melbourne	322	300	(93.2%)
Escourrou et al.	1984	Toulouse	443	407	(91.7%)
Neoptolemos et al.	1984	Leicester	100	98	(98.0%)
Davidson et al.	1988	Leicester	106	105	(99.0%)
Rosseland & Solhaug	1988	Norway/Sweden	75	75	(100%)

NOTE: "Success" refers only to cannulation of the papilla and incision of the sphincter of Oddi. See Table 2 for statistics on the success rates of stone extraction.

Table 2: Reported success rates of common bile duct stone removal following endoscopic papillotomy.

Investigator(s)	Date	Att Pap	Succ Pap	Clear Stone	Succ Rate	Overall Success
Classen & Safrany	1975	--	39	33	84.6%	--
Safrany	1977	--	185	173	93.5%	--
Koch et al.	1977	231	222	192	86.5%	83.1%
Safrany	1978	--	3070	2779	90.5%	--
Ligoury & Loriga	1978	145	--	120	--	82.8%
Montori et al.	1979	--	155	149	96.1%	--
Nakajima et al.	1979	446	430	370	86.0%	83.0%
Cotton	1980	134	129	119	92.2%	88.8%
Siegel	1981	235	230	228	99.1%	97.0%
Viceconte et al.	1981	238	205	195	95.1%	81.9%
Cotton & Vallon	1981	679	590	513	86.9%	75.6%
Mee et al.	1981	71	69	65	94.2%	91.5%
Cotton & Vallon	1982	71	70	61	87.1%	85.9%
Kawai et al.	1983	422	413	398	96.4%	94.3%
Neoptolemos et al.	1984	100	98	91	92.9%	91.0%
Rosseland & Solhaug	1988	75	75	71	94.6%	94.6%

Abbreviations: **Att Pap** = Number of papillotomies attempted for treatment of choledocholithisis; **Succ Pap** = Number of attempts in which section of the sphincter of Oddi was achieved; **Clear Stone** = Number of cases in which spontaneous passage or direct extraction of common duct stones was confirmed; **Succ Rate** = Percentage of cases in which clearance of stones was confirmed following a successful papillotomy; **Overall Success** = Percentage of all attempted cases (both successful and failed papillotomies) in which clearance of stones from the common duct was achieved; -- = Data not given.

5) impaction of an extraction basket at the papilla. Immediate complications usually respond to supportive treatment, necessitating emergency surgery in from 0.5-5.7% (average 1-2.5%) of patients after successful papil-lotomy.[27-35,37,39-45,47,49-52,54,55] Mortality from this procedure varies from 0-4.7%, with most large studies reporting death rates of 0.8-1.7%.[27-30,32-37,39-45,47,50-55] Table 3 provides data regarding the complication and death rates of endoscopic papillotomy reported in several series.

Comparison of success and complication rates of surgical versus endoscopic treatment is difficult, mainly because of significant differences in patient selec-tion.[31,56-59] The majority of persons referred for endo-scopic papillotomy are old and/or relatively ill, and thus represent poor candidates for surgery. In such high risk patients, endoscopic biliary decompression avoids the surgical complications related to laparotomy, duodenotomy, and general anesthesia.[32,34,37,42,55] In young and healthy patients the morbidity and mortality of surgical and endo-scopic therapy are similar,[35,41,47,59] and the preferred form of treatment is often determined by the individual concerns of the patient and physician. Endoscopic papil-lotomy offers the short term advantages of lower cost, avoidance of surgical risk, and shorter hospitalization time. However, the potential long-term consequences of 1) sphincter ablation, and 2) leaving behind a stone filled gallbladder, are undetermined.

Table 3: Reported early morbidity and mortality from endoscopic papillotomy.

Investigator(s)	Date	N	Comp	Surg	Death
Safrany	1977	243	24 (9.9%)	6 (2.5%)	3 (1.2%)
Koch et al.	1977	254	19 (7.5%)	8 (3.1%)	2 (0.8%)
Safrany	1978	3618	254 (7.0%)	83 (2.3%)	50 (1.4%)
Siefert	1978	880	64 (7.3%)	19 (2.2%)	15 (1.7%)
Reiter et al.	1978	1403	103 (7.3%)	33 (2.4%)	21 (1.5%)
Ligoury & Loriga	1978	144	21 (14.6%)	2 (1.4%)	1 (0.7%)
Montori et al.	1979	194	13 (6.7%)	1 (0.5%)	1 (0.5%)
Nakajima et al.	1979	485*	37 (7.6%)	6 (1.2%)	2 (0.4%)
Cotton	1980	129	10 (7.8%)	6 (2.3%)	1 (0.8%)
Geenen et al.	1981	1250*	109 (8.7%)	23 (1.8%)	15 (1.2%)
Siegel	1981	258	14 (5.4%)	2 (0.8%)	2 (0.8%)
Viceconte et al.	1981	255	18 (7.1%)	1 (0.4%)	2 (0.8%)
Cotton & Vallon	1981	590	58 (9.8%)	11 (1.9%)	7 (1.2%)
Mee et al.	1981	69	9 (13.0%)	3 (4.3%)	0 (0%)
Cotton & Vallon	1982	70	6 (8.6%)	2 (2.9%)	0 (0%)
Kawai et al.	1983	496*	17 (3.4%)	6 (1.2%)	2 (0.4%)
Roberts-Thompson	1984	300	14 (4.7%)	3 (1.0%)	0 (0%)
Escourrou et al.	1984	407	27 (6.6%)	7 (1.7%)	6 (1.5%)
Neoptolemos et al.	1984	98	13 (13.3%)	--	1 (1.0%)
Leese et al.	1985	394*	41 (10.4%)	15 (3.8%)	3 (0.8%)
Davidson et al.	1988	106*	21 (19.8%)	6 (5.7%)	5 (4.7%)
Rosseland & Solhaug	1988	75	10 (13.3%)	2 (2.6%)	1 (1.3%)

Abbreviations: **N** = Total number of papillotomies performed (or attempted, see below) in the series; **Comp** = Number and percentage of early complications following the procedure; **Surg** = Number and percentage of patients requiring emergency surgery for treatment of immediate complications; **Death** = Number (and percentage) of deaths directly related to papillotomy; -- = Data not given.

*These studies report morbidity and mortality rates of all attempted papillotomies (as opposed to all successful procedures). If complications and deaths occurred only among patients who underwent successful papillotomy, then the percentages reported in these series are slightly lower than the comparable rates given in the other studies.

Endoscopic papillotomy is contraindicated in certain situations, such as the presence of: 1) uncorrectable coagulation disorders, 2) long distal common duct strictures, and 3) abnormalities of the proximal bile ducts unapproachable endoscopically.[27,30,32,37,41-43,60] Some endoscopists consider large stones (greater than 20-25 mm in diameter) and juxta-ampullary diverticula relative contraindications, since these conditions increase the difficulty of stone extraction and cannulation, respectively.[30,32,36,37,41,43,47,60] Some endoscopists have successfully used crushing and lithotripter baskets to fragment and remove large stones.[31,36,56,60-62] Acute pancreatitis has been considered a contraindication to papillotomy by some authors,[30,32,37,43] but others have used this technique effectively to treat acute gallstone pancreatitis.[41,47-49]

Papillotomy in Patients with an Intact Gallbladder:

Initially, endoscopic papillotomy was used primarily to treat patients with retained or recurrent common duct stones after cholecystectomy.[31,43,63] In this setting, endoscopic therapy offered a clear advantage over re-operation. The use of endoscopic treatment was questioned, however, in patients with an intact gallbladder. For years surgeons had cautioned that permanent destruction of the sphincter of Oddi could lead to later complications if the gallbladder was left in

place. Frequent development of acute and chronic inflamma-
tory changes in the gallbladder wall, often accompanied by
stones and uniformly associated with bacterial infection,
has been described after surgical sphincterotomy and chole-
dochoenterostomy in both dogs[64-67] and humans.[68] Investi-
gators attributed this outcome to the ascent of pathogens
from the duodenum, with the gallbladder acting as a
reservoir of infection. Thus, surgeons have long advocated
cholecystectomy when performing biliary bypass surgery or
sphincter ablation.[12,68-70] According to Jones,[12] "the gall-
bladder cannot fill and function normally in the absence of
the distal sphincters, and if it is left behind, stasis and
infection may develop." As a result, endoscopic papillotomy
without cholecystectomy was initially reserved for patients
considered poor surgical candidates, due to age and/or
coexisting illness.[27,32-34,37,43,55] In such cases the
immediate advantages of endoscopy over surgery outweighed
the potential long-term risks of leaving the gallbladder *in
situ* in the presence of a nonfunctional sphincter of Oddi.

With further experience, however, endoscopic papil-
lotomy has been employed increasingly in patients with a
gallbladder *in situ*. Upon recovery, many such persons are
discharged with their gallbladder in place. The percentage
of patients left with an *in situ* gallbladder after papil-
lotomy varies widely among different centers, ranging from
6-61%[27-30,32,34,35,37,39-42,44,45,47,50-52,57,63,71-73] (see
Table 4). Management of these individuals has been a subject

Table 4: Percentage of papillotomies performed on patients with an intact gallbladder.

Investigator(s)	Date	Center	# Pap	# GB	% GB
Safrany	1977	Munster	185	39	21.1%
Safrany	1978	15 International	3070	887	28.9%
Siefert	1978	9 German	743	171	23.0%
Reiter	1978	9 German	1403[*]	--	20.5%
Ligoury & Loriga	1978	Paris	145[**]	73	50.3%
Montori et al.	1979	8 Italian	194[*]	19	9.8%
Nakajima et al	1979	25 Japanese	430	154	35.8%
Cotton	1980	London	129	15	11.6%
Geenen et al.	1981	21 U.S.	1106	93	8.4%
Siegel	1981	New York	230	15	6.5%
Viceconte et al.	1981	Rome	254[*]	41	16.1%
Cotton & Vallon	1981	14 British	679[**]	70	10.3%
Mee et al.	1981	London	71[**]	15	21.1%
Cremer et al.	1981	Brussels	809[*]	496	61.3%
Cotton & Vallon	1982	London	310	71	22.9%
Roberts-Thompson	1984	Melbourne	227	51	22.5%
Escourrou et al.	1984	Toulouse	407	234	57.5%
Leese et al.	1985	Leicester	319	--	58%
Kullman et al.	1985	Sweden	202[*]	101	50.0%
Tulassay & Papp	1985	Budapest	525[*]	131	25.0%
Thompson	1986	Bristol	64	23	35.9%
Jacobsen & Matzen	1987	Copenhagen	96	44	45.8%
Siegel et al.	1988	Wilhelmshaven/N.Y.	4177[*]	1272	30.5%

Abbreviations: # Pap = Number of successful papillotomies performed (or attempted, as noted) for choledocholithiasis (does not include procedures performed for other indications, except when noted, see below); # GB = Number of papillotomies performed (or attempted) on patients with an intact gallbladder; % GB = Percentage of patients undergoing papillotomy with a gallbladder in place.

[*] Includes papillotomies performed for choledocholithiasis as well as other indications.

[**] Statistics refer to the number of papillotomies attempted; data on the number of procedures successfully performed in patients with a gallbladder is not given.

of debate. Initially, the potential long-term risk of chole-
cystitis led some experts to recommend elective cholecystec-
tomy after papillotomy.[74-76] Rösch *et al.*[75] in 1981
professed that "Late complications must be expected in
patients with gallbladder *in situ*; cholecystectomy is there-
fore advisable in papillotomized patients after improvement
of their general condition." However, many clinicians now
consider pre-emptive surgery in asymptomatic individuals
unwarranted.[31,52,53,55,63,77-79] Riemann *et al.*[77] in 1983
stated that "The idea . . . that, following endoscopic
papillotomy, the gallbladder should . . . be extirpated,
since the loss of function of the gallbladder after sphinc-
terotomy, possibly in conjunction with the ascent of
bacteria, would promote cholecystitis, can now be dropped."
However, the authors still cautioned that sphincter ablation
may lead to very long-term sequelae in young persons.

Follow-up data on patients with an intact gallbladder
after papillotomy are quite variable. Table 5 shows the
results of several series on patients undergoing papillotomy
with a gallbladder in place. The incidence of acute chole-
cystitis in this population varies from 0-16.7%, and the
rate of subsequent cholecystectomy ranges from
0-26.7%.[38,51-55,59,63,72-83] Comparison of these statistics
is difficult, however, because of non-standard methods of
reporting. Many studies report the rate of cholecystectomy
after papillotomy, but not all investigators distinguish
between prophylactic elective operation in asymptomatic

Table 5: Long-term follow-up of patients with an intact gallbladder after endoscopic papillotomy.

Investigator(s)	Date	F/U Period Range (Mean)	N	# (%) Cholecystectomy: Elective	Symptoms	Total	Chole- cystitis
Hagenmüller et al.	1979	1-4y	68	-	7 (10.3%)	7 (10.3%)	6 (8.8%)
Cotton	1980	3-36m	8	*	1 (12.5%)	-	2 (25%)
Rösch et al.	1981	2-7y	101	-	-	23 (22.8%)	-
Cremer et al.	1981	-	496	4%	4%	-	6%
Safrany et al.	1982	2-8y	352	76 (21.6%)	18 (5.1%)	94 (26.7%)	40 (11.4%)
Cotton & Vallon	1982	4m-5y (19m)	70	11 (15.8%)	5 (7.1%)	16 (22.9%)	2 (2.9%)
Riemann et al.	1983	2-9y	206	24 (11.7%)	15 (7.3%)	39 (18.9%)	-
Escourrou et al.	1984	6-66m (22m)	130	-	7 (5.4%)	-	8 (6.2%)
Neoptolemos et al.	1984	4-50m (17m)	38	-	1 (2.6%)	1 (2.6%)	1 (2.6%)
Solhaug et al.	1984	2w-60m (28m)	22	3 (13.6%)	-	-	-
Winstanley et al.	1985	18-76m	22	-	-	0 (0%)	-
Siegel	1985	up to 7y	212	-	-	-	-
Tulassay & Papp	1985	up to 1y	131	-	-	-	10 (7.6%)
Martin & Tweedle	1987	12-44m (24m)	70	5 (7.1%)	4 (5.7%)	9 (12.9%)	-
Tanaka et al.	1987	-	122	**	3 (2.5%)	8 (6.6%)	5 (4.1%)
Jacobsen & Matzen	1987	2-81m (4.1y)	44	-	1 (2.3%)	-	0 (0%)
Worthley & Toouli	1988	2-42m	20	-	3 (15%)	8 (40%)	5 (25.0%)
Davidson et al.	1988	1-8y (30m)	85	1 (1.2%)	6 (7.1%)	7 (8.2%)	3 (3.5%)
Siegel et al.	1988	***	1272	-	133 (10.5%)	-	111***
Miller et al.	1988	- (28m)	34	-	7 (20.6%)	7 (20.6%)	-
Rosseland & Solhaug	1988	5-8y	66	2 (3.0%)	11 (16.7%)	13 (19.7%)	11 (16.7%)

<u>Abbreviations:</u> **F/U Period** = period of follow-up (range and mean); **N** = Total number of patients; **# (%) Cholecystectomy** = Number and percentage of patients undergoing subsequent cholecystectomy; **Elective** = patients undergoing elective operation, mostly for prophylactic excision of the gallbladder, but some studies may include patients undergoing "elective" (i.e., non-emergent) surgery for symptomatic biliary illness; **Symptoms** = patients operated on for biliary symptoms (including, but not limited to, acute cholecystitis); **Cholecystitis** = number and percentage of patients developing cholecystitis after papillotomy (not all studies specify acute vs. chronic cholecystitis); - = Data not given.

*A total of 12 patients with an intact gallbladder underwent papillotomy, early elective prophylactic cholecystectomy was performed in 4 (33%), leaving 8 persons available for long-term follow-up.

**This study was based on a total of 162 patients, 40 of whom (24.7%) underwent prophylactic cholecystectomy electively shortly after papillotomy (all of them had documented gallstones).

***Of these 111 patients, 109 (8.6% of 1272) developed acute cholecystitis within 10 days of papillotomy. Two of 337 patients (0.6%) followed for 8-13 years died of complications of recurrent cholecystitis.

persons and surgery for cholecystitis or biliary symptoms. Also, a significant percentage of patients require cholecystectomy early (within one month) after papillotomy. Some studies include these cases in follow-up statistics, while other exclude these data as not representative of "long-term" outcome. Since endoscopic papillotomy has only been in use for fifteen years, follow-up information is limited. Many investigators believe that definitive conclusions (especially regarding young patients with a relatively long life expectancy after papillotomy) must await longer study periods.

Predicting Gallbladder Disease After Papillotomy:

Some investigators have attempted to define predictive factors for the development of cholecystitis after endoscopic papillotomy. Cotton[56] in 1984 first proposed that an obstructed cystic duct noted at the time of papillotomy may lead to eventual gallbladder complications. Solhaug et al.[80] reported follow-up data on 22 patients with an intact gallbladder at the time of papillotomy, twelve of whom demonstrated a lack of gallbladder filling on ERCP. After a two week to 60 month (median 28 month) follow-up period, four (33%) of these twelve patients required cholecystectomy for biliary symptoms. After six months to nine years of follow-up, Tanaka et al.[82] in 1987 noted the occurrence of acute cholecystitis in two (33%) of six patients with a previously

non-visualized gallbladder, and in three (12%) of 25 persons
with documented gallstones. No instances of acute cholecys-
titis were seen among 91 patients with stone-free gall-
bladders at ERCP. The authors thus stated that "cholecystec-
tomy should be advocated . . . in patients with gallstones
or nonvisualization of the gallbladder after endoscopic
sphincterotomy due to the high incidence of acute cholecys-
titis in this subgroup." Worthley and Toouli[83] in 1988 noted
a lack of gallbladder opacification on ERCP in eight of
twenty patients. Six (75%) of these eight required cholecys-
tectomy for acute cholecystitis within three to 28 months
(median seven months), and three died postoperatively. Two
(16.7%) of the twelve individuals whose gallbladders filled
required cholecystectomy shortly after papillotomy, and the
other ten persons remained symptom-free after a 2-42 month
(median nine month) follow-up period. The authors concluded
that "Should the gallbladder fail to opacify despite free
cannulation of the common bile duct, dense opacification of
the extrahepatic biliary tree and filling of the tertiary
intrahepatic bile ducts, then cholecystectomy is recommended
to avoid future gallbladder complications."

However, not all studies agree on this point. Martin
and Tweedle[81] in 1987 reported on 70 patients with gall-
bladders whose common ducts were cleared of stones at papil-
lotomy. Of four patients who required cholecystectomy for
symptoms within six months, three (75%) demonstrated gall-
bladder visualization on ERCP. The authors also commented on

one patient who subsequently required surgery despite having no evidence of gallstones (either before or after cholecystectomy), and thus stated that "We have not been able to correlate any clinical, endoscopic or radiological variable with the need for surgery."

There is also disagreement as to whether a lack of gallbladder opacification on ERCP is truly indicative of cystic duct obstruction, as Cotton has claimed.[84] Rohrmann et al.[85] in 1979 followed 63 patients with this finding. At surgery or autopsy, 35 (55.6%) had a distal common bile duct obstruction (with no abnormality of the cystic duct or gallbladder), nineteen (30.2%) had obstructing lesions of the cystic duct or gallbladder (with normal common ducts), eight (12.7%) had biliary obstruction at the junction of the cystic and common hepatic ducts, and one patient (1.6%) had a normal biliary tree. This study demonstrates that non-filling of the gallbladder on ERCP does not necessarily imply cystic duct obstruction, but may be related to sludging and stasis of bile caused by a distal common duct lesion. Since papillotomy is nearly always performed in the setting of common duct obstruction, it follows that ERCP observations cannot be used to determine cystic duct patency. Of course, this conclusion does not invalidate the value of this particular finding for predicting future gallbladder complications. Regardless of the meaning of an unfilled gallbladder on ERCP, the reliability of this sign as a predictor for subsequent disease depends upon

statistical correlation with long-term outcomes. Studies with larger series and longer follow-up periods are necessary before definite conclusions can be drawn.

The most important risk factor for the development of acute cholecystitis is the presence of stones in the gall-bladder. Although few studies have reported the incidence of gallbladder calculi in patients undergoing papillotomy, gallstones are likely present in the majority of such persons. Tanaka et al.[82] noted gallstones in 65 (40%) of 162 papillotomy patients with an intact gallbladder. However, one European[72] study quoted a lack of cholelithiasis in 46 (9%) 496 cases, and a large European and American study[63] found 1208 (95%) of 1272 such patients to have demonstrable gallbladder stones at the time of papillotomy. This varia-bility may be related to the prevalence of gallstones in Asian versus Western populations. After papillotomy, however, the pathophysiological significance of gallstones may be diminished, since patients often pass gallbladder stones spontaneously following destruction of the sphincter of Oddi.[51,55,56,63,80,82] A recent study corroborated this observation by demonstrating that papillotomy facilitated the passage of glass beads placed into canine gall-bladders.[86] Not surprisingly, small beads passed with much greater frequency than large ones. Even after sphincter ablation, any single stone of sufficient size can lodge in the cystic duct and lead to cholecystitis.

It is also possible that individuals may continue to form gallstones after papillotomy. Data on this subject is contradictory. Cohn *et al.*[87] noted increased lithogenicity (for cholesterol stones) of gallbladder bile following sphincterotomy in dogs. However, Hutton *et al.*[88] found a decreased incidence of gallstones in prairie dogs after papillotomy. It is not clear what changes take place in human bile after sphincter ablation. Matsumoto and Tanaka[82,89] reported the subsequent formation of calcium bilirubinate gallstones (demonstrated by ERCP and proven by cholecystectomy) in two patients who had no stones evident radiographically at the time of papillotomy. Since pigment calcium gallstones have been associated with infected bile (one study noted positive bacterial cultures from gall-bladder bile in 80% of cases of calcium bilirubinate gall-stones[90]), the authors suggested that ascending infection of the biliary tract could have contributed to stone formation. Incidentally, one could argue that in isolated cases, "new" gallstones might represent stones that were missed on initial ERCP. However, that is unlikely in these instances, since calcified pigment stones are usually apparent on plain radiographs. At any rate, numerous follow-up studies have found that acute cholecystitis does occur after papillo-tomy.[51-55,59,63,71-72,74,76,77,79,82,83]

Radiologic Diagnosis of Acute Cholecystitis:

Characteristic clinical and laboratory findings of acute cholecystitis include: 1) a history of right upper quadrant pain (often precipitated by a fatty meal), anorexia, nausea, vomiting, and fever; 2) abdominal tenderness, inspiratory arrest on deep palpation over the gallbladder (Murphy's sign), a palpable gallbladder, and fever on physical examination; and 3) an elevated leukocyte count. Although classic, such signs and symptoms are by no means specific for this disease. The differential diagnosis of right upper quadrant abdominal pain includes such conditions as appendicitis, pancreatitis, perforated ulcer, bowel ischemia, diverticulitis, mesenteric adenitis, acute hepatic congestion, hepatic mass lesions, gonococcal perihepatitis, renal colic, pyelonephritis, ovarian torsion, ruptured ectopic pregnancy, pneumonitis, and acute myocardial infarction.[9,91,92] Appropriate radiologic procedures are necessary to confirm the presence of gallbladder disease before instituting surgical therapy. Currently employed diagnostic imaging studies for detecting acute cholecystitis include ultrasonography and cholescintigraphy. Older biliary imaging modalities such as oral cholecystography and intravenous cholangiography are now rarely used in this clinical setting.

Sonographic diagnosis of cholelithiasis was first reported in 1963.[93] Ultrasonography has since become a

valuable tool in biliary tract imaging. Sonography is extremely sensitive for detecting stones in the gallbladder. However, this observation does not constitute proof of acute cholecystitis, since many people (an estimated 15-20 million Americans) have "silent" gallstones.[10,92] Biliary sonographers have therefore defined a spectrum of findings associated with an abnormal gallbladder. Major sonographic criteria indicative of gallbladder disease include: 1) the presence of gallstones, or 2) a non-visualized gallbladder (implying a shrunken and diseased organ, usually seen in chronic cholecystitis). Various ancillary sonographic findings have been associated with acute gallbladder illness. These so-called minor criteria for acute cholecystitis include: 1) intramural sonolucency (representing edema of the gallbladder wall), 2) pericholecystic inflammation or abscess, 3) tenderness over the gallbladder elicited by the transducer (sonographic Murphy's sign), 4) gas in the gallbladder wall or lumen, 5) thickening of the gallbladder wall, 6) gallbladder distension, and 7) sludge.[92,94] In most studies, ultrasonography utilizing only major criteria is 81-86% sensitive in confirming a clinical suspicion of acute cholecystitis, and has a specificity of 94-98%. Adding minor criteria increases the sensitivity to 90-98%, but lowers the specificity to 70-76%.[92,94] The limitation of ultrasound in diagnosing acute cholecystitis is that this imaging technique provides only anatomic information, and cannot assess the functional patency of the cystic duct.

Cholescintigraphy using ^{99m}Tc-labelled tracers was introduced in the mid-1970's.[95,96] This nuclear imaging modality involves intravenous injection of a radioactive tracer selectively taken up by hepatocytes and excreted into the bile. Currently used radiopharmaceuticals include several chemical derivatives of iminodiacetic acid (IDA). These agents are organic anions chelated to a ^{99m}Tc atom, which cross hepatocyte membranes by a carrier-mediated transport mechanism, similar to bilirubin uptake. The liver removes 80-85% of the administered dose of tracer from the bloodstream (the remainder undergoes renal excretion), and IDA derivatives are secreted unmodified into bile canaliculi.[92,95,97,98] Following injection of radioisotope, serial images obtained with a gamma camera depict the flow of labelled bile through the hepatobiliary system. Figure 5 is a schematic diagram depicting the hepatobiliary transit of ^{99m}Tc-IDA agents. In a normal study, liver uptake occurs rapidly, followed by appearance of tracer in the bile ducts, gallbladder, and intestine within one hour. The classic scintigraphic finding in acute cholecystitis is a lack of visualization of the gallbladder, in the presence of normal visualization of the bile ducts and bowel, indicative of a blocked cystic duct.[92,94,97-99] Cholescintigraphy is performed after a fast of at least two hours (preferably overnight), in order to prevent false positive scans due to gallbladder contraction stimulated by a recent meal.

Labels in figure: Sinusoid, Albumin, Albumin-Tc^{99m}IDA Complex, Tc^{99m}IDA, Hepatocyte, Canaliculus, Bile duct, Liver, Gallbladder, Common Bile duct, Duodenum
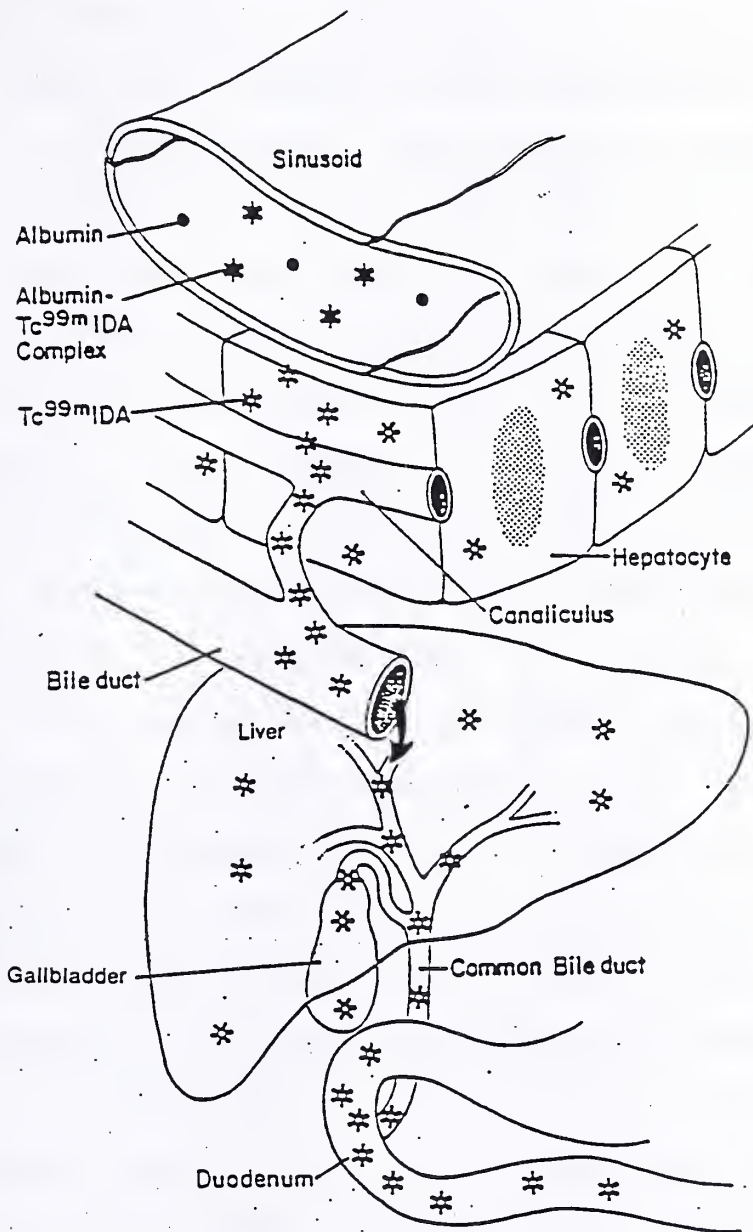
Figure 5: Schematic diagram of the flow of ^{99m}Tc-IDA derivatives through the hepatobiliary system. Tracer is loosely bound to albumin in the bloodstream, and enters hepatocytes by a carrier-mediated transport mechanism. ^{99m}Tc-IDA compounds are secreted unconjugated into bile canaliculi. (Modified from Krishnamurthy, 1988.[98])

The reported sensitivity of cholescintigraphy for detecting acute cholecystitis ranges from 85-100%, with most studies reporting values of 95-98%. Specificity varies from 70-100% in clinical series, with typically reported values around 90-97%.[92,94,100-118] These data are summarized in Table 6. False negative tests can occur in cases of acute acalculous cholecystitis. Delayed gallbladder visualization (between one and four hours) also occurs rarely in acute cholecystitis. This finding is usually associated with chronic cholecystitis. Nonvisualization of the gallbladder has been observed in the following conditions: 1) chronic cholecystitis, 2) pancreatitis, 3) severe intercurrent illness, 4) alcoholism, 5) prolonged fasting, 6) lack of adequate fasting, 7) hyperalimentation, 8) trauma, and 9) gallbladder neoplasms.[92,94,97,99] In most series, however, false positive tests for acute cholecystitis are rare.

Numerous studies have compared the relative utility of ultrasonography and cholescintigraphy in detecting gall-bladder disease.[105,106,109-111,113,114,116-120] These investigations are not fully comparable, due to: 1) differences in study design and patient selection (prospective vs. retrospective); 2) variability in imaging technique, such as equipment used (static vs. real time ultrasonography), sonographic criteria chosen for acute cholecystitis, the particular radiopharmaceutical used, and timing of scintigraphy (i.e., how long the test was carried out); and 3) different methods of follow-up, including means

Table 6: Results of ^{99m}Tc-IDA cholescintigraphy in diagnosing acute cholecystitis.

Investigator(s)	Date	Sensitivity	Specificity
Weissman et al.	1979	95%	100%
Freitas et al.	1980	100%	90%
Suarez et al.	1980	97.6%	75%
Szlabick et al.	1980	100%	97.6%
Freitas & Gulati	1980	97%	87%
Zeman et al.	1981	98%	81%
Worthen et al.	1981	95%	100%
Weissman et al.	1981	95.2%	99.2%
Hall et al.	1981	100%	70%
Freitas et al.	1982	98.3%	90.2%
Shuman et al.	1982	86%	73%
Ralls et al.	1982	85.7%	83.9%
Mauro et al.	1982	100%	94%
Matolo et al.	1982	93%	100%
Freitas et al.	1983	100%[*]	85.1%[*]
		95.3%[**]	98.6%[**]
Samuels et al.	1983	97%	93%
Cabellon et al.	1984	100%	96%
Gill et al.	1985	100%	100%
Fink-Bennett et al.	1985	97%	--

[*] Using "strict" criteria for acute cholecystitis (pathologically demonstrated transmural acute inflammatory infiltrates), and gallbladder visualization time (within 1 hour).

[**] Using "liberal" criteria for acute cholecystitis (any of the following: transmural acute inflammatory infiltrates, hemorrhagic necrosis of gallbladder wall or mucosa, complete cystic duct obstruction, or postcholecystectomy relief of pain/fever/leukocytosis); and gallbladder visualization time (within 4 hours).

of proving the final diagnosis (clinical vs. pathological), and the specific pathologic criteria used to define acute vs. chronic cholecystitis. Only two studies[106,110] recommended sonography as the initial diagnostic procedure of choice for suspected acute cholecystitis. Most investigators[105,109,111,113,114,116-120] found scintigraphy more sensitive than sonography in detecting acute cholecystitis, and thus recommended cholescintigraphy as the most appropriate initial test in this setting. Marton and Doubilet[94] recently performed an extensive review of the literature and reached the same conclusion. They suggested using ultrasonography first for evaluating patients suspected of having chronic gallbladder disease, and cholescintigraphy first in suspected cases of acute cholecystitis (defined as acute inflammation accompanied by cystic duct obstruction). Most experts agree that ^{99m}Tc-IDA cholescintigraphy represents the "gold standard" for the radiologic confirmation of clinically suspected acute cholecystitis.

Cholescintigraphy in the Setting of Sphincter Ablation:

Cholescintigraphy is an excellent diagnostic test for acute cholecystitis in patients with an intact biliary system. Its efficacy, however, has not been studied after endoscopic papillotomy in humans. In this setting, lack of resistance at the terminal common bile duct may allow bile to flow completely unimpeded into the duodenum, bypassing

the gallbladder entirely. It is therefore possible that the gallbladder may not visualize following sphincter ablation, even if the cystic duct is patent. A false positive test for acute cholecystitis is potentially dangerous, since such diagnostic data could form the basis of a decision to operate on an acutely ill patient. Studies have found that patients with acute cholecystitis benefit from early cholecystectomy.[121-124] Many surgeons thus favor rapid diagnosis and operative treatment of this disease. The majority of persons with an intact gallbladder treated with papillotomy are elderly, and therefore subject to great risk from emergency surgery. This study was undertaken to assess baseline cholescintigraphic findings in individuals with an *in situ* gallbladder after endoscopic papillotomy. By determining whether or not the gallbladder visualizes in such persons when they are clinically asymptomatic, one can ascertain the reliability of this diagnostic modality for detecting acute cholecystitis in patients who have undergone papillotomy. Since cholescintigraphy measures gallbladder filling, knowledge of the mechanism of this process will allow a more complete understanding of the utility and limitations of this imaging method in different populations.

Possible Mechanisms of Gallbladder Filling:

The earliest theory of gallbladder function ascribed control of the filling process to the sphincter of Oddi.

Between meals the majority of secreted bile enters the gall-
bladder for storage. It was thus thought that tonic contrac-
tion of the sphincter during fasting diverted all bile into
the gallbladder. Observations of a biliary sphincter date
back to Vesalius, who noted a membrane at the distal orifice
of the common bile duct, which he believed prevented reflux
of duodenal contents into the biliary tree. Glisson proposed
the existence of a choledochal sphincter in 1681. In 1879
the zoologist Gage provided the first anatomic description
of this muscle in the cat. Oddi subsequently demonstrated
the presence of a common duct sphincter in several animal
species in 1887, and in 1898 Hendrickson described this
structure in man.[4,125] From these early observations,
medical scientists concluded that this terminal sphincter
was the means of regulating bile flow from the gallbladder
to the intestine. It seems perfectly logical that, when the
sphincter closes, the rising pressure in the common duct
would force bile into the gallbladder. In this model the
gallbladder acts as a capacitance organ, a low pressure
reservoir which expands to accommodate the continuous flow
of bile into a closed system. Gallbladder filling is
therefore an entirely passive process. This mechanism is
described in numerous medical texts.[3,8,126-131] Alterna-
tively, some researchers have proposed that contraction of
the duodenal musculature (either instead of, or in addition
to, sphincter activity) may be responsible for generating
the pressure necessary for gallbladder filling.[132-135]

Numerous clinical and laboratory studies, however, have suggested that filling of the gallbladder may be mediated by a more complex network of physiologic interactions, under autonomic and hormonal control. Utilizing techniques such as gallbladder and sphincter of Oddi manometry,[136-138] bile flow measurement,[139-141] electromyography,[136,140-143] cineradiography,[142,144] and biliary scintigraphy,[145-147] researchers have found evidence of periodic gallbladder and sphincter motor activity in the interdigestive state. These findings have been reported in humans,[137-139,142,144-146] dogs,[136,140] prairie dogs,[146,147] and opossums.[143] During fasting, the gallbladder does not fill at a constant rate; it is subject to fluctuations of bile flow and often undergoes partial contraction. These variations in biliary motility are regular and occur in synchrony with the intestinal migrating myoelectric complex (MMC).[136,140-142] The MMC is a rhythmic pattern of myoelectric, motor, and secretory activity which propogates in a caudad direction along the entire small bowel from antrum to terminal ileum.[148] Thus, rather than relying exclusively upon biliary pressure, contractions and relaxations of the gallbladder wall musculature could act to forcibly pump bile into the sac. The spiral valves of the cystic duct may also play a role. In this model the gallbladder becomes an active participant in the filling process, functioning as a bellows. Experimental evidence has been found which suggests both active and passive modes of gallbladder filling.

Experimental Studies of Gallbladder Filling:

Radiographic imaging of the gallbladder by intravenous injection of tetrabromophenolphthalein was first described in 1924.[149] Copher[150] in 1925 reported that gallbladder opacification required an intact choledochal sphincter. "Experimentally and clinically, the retention of the bile in the biliary tract by the sphincter of the common duct is necessary to secure good shadows of the gallbladder." Cannulation of the common bile duct in dogs resulted in a lack of visualization of the gallbladder by intravenous cholecystography. Copher explained this finding by proposing that "canalization of the common duct permitted free outflow of bile from the liver," thereby implying that some distal resistance to bile flow was necessary for the gallbladder to fill. In 1926 Copher *et al.*[133] subjected dogs to cholecystectomy and anastomosed a thin rubber bag to the cystic duct. Subsequent intravenous cholecystography demonstrated opacification of this artificial gallbladder. Since rubber bags obviously possess no intrinsic motor activity, filling must have occurred passively, as a result of biliary pressure. Unfortunately, Copher did not repeat this experiment in sphincterotomized animals, which would have demonstrated whether or not the sphincter of Oddi was important in generating the necessary pressure.

Burget[151] in 1925 measured changes in flow resistance in the common bile duct in dogs in response to

administration of pilocarpine, physostigmine, atropine, and epinephrine. Pilocarpine and physostigmine increased biliary pressure, while atropine and epinephrine caused a fall in biliary pressure. Burget attributed these effects to the pharmacologically induced changes in intestinal motor tone. In a subsequent experiment,[134] he performed the same measurements after transecting the common duct immediately proximal to the sphincter of Oddi and then directing the duct into the duodenum through a surgically created orifice. This effectively eliminated the sphincter, while preserving the structure of the duodenal musculature surrounding the distal common bile duct. Burget found similar effects on biliary pressure following drug adminstration in this second set of dogs. He thus concluded that "The sphincter of Oddi is probably not at all concerned in the regulation of the flow of bile, at least not in animals where the duct enters the duodenal musculature obliquely."

Like Copher, Whitaker[132] in 1926 noted a lack of gall-bladder visualization in dogs following intravenous injec-tion of tetraiodophenolphthalein after cannulation of the common bile duct. Upon surgical ablation of the sphincter, however, he obtained normal cholecystograms in three dogs. Patency of the choledochal orifice was confirmed at autopsy in one dog. Whitaker thus stated that "This seems to show that an actual sphincteric action at the papilla is not necessary to the filling of the gallbladder, but that other factors, such as pressure of the intestinal musculature

where the duct passes through, possibly serve this function." Interestingly, no gallbladder filling was noted after cutting the sphincter in five cats. The author made no attempt to explain these contradictory findings, which may have been due to species variation.

In 1952, Jones and Smith[70] performed follow-up imaging studies in three patients with intact gallbladders after transduodenal sphincteroplasty (for treatment of recurrent pancreatitis). Before surgery, all three individuals had normally functioning gallbladders by cholecystography. At operation, all three gallbladders appeared grossly normal, with no palpable stones. The common bile duct was explored and found to be free of stones in two patients. Cholecysto-graphy performed at two, three and a half, and four months postoperatively revealed non-opacifying gallbladders in all three individuals. In one person reflux of barium into the common duct was seen on upper GI examination (confirmation of sphincter incompetence). Data from this small series suggest that either: 1) the sphincter of Oddi plays a prominent role in gallbladder filling in humans, or 2) sphincter ablation predisposes to gallbladder disease. Both conclusions may be true and causally related.

In 1960 Lempke[135] performed oral cholecystography in eight patients who had undergone either surgical sphincter-otomy or sphincter resection with biliary-enteric anastomosis. In contrast to Jones' and Smith's observations, opacification of the gallbladder occurred in six of eight

individuals between two weeks and 21 months after surgery. In the remaining two patients the gallbladder visualized, but demonstrated decreased concentration of contrast as compared to preoperative studies. In three patients (two of whom had normal cholecystograms) postoperative sphincter incompetence was suggested by the presence of air in the bile ducts on roentgenography (one case) or reflux of barium into the common duct on upper GI studies (two cases). To explain these findings, Lempke proposed that gallbladder filling could have resulted from the resistance to bile flow provided by 1) the duodenal musculature, 2) partial obstruction due to biliary sediment (noted in one case), 3) extrinsic pressure from an indurated pancreatic head (noted in one case), or 4) restenosis of the papillary orifice. However, he ultimately concluded that "these observations . . . cast some doubt on the significance of the sphincter of Oddi in gallbladder function in man."

Tansy et al.[152] in 1974 performed a series of experiments to ascertain the role of the intramural common bile duct in gallbladder filling in dogs. They measured gallbladder filling directly by timed aspiration of bile through a catheter inserted into the fundus. For comparison, cannulation of a hepatic duct allowed determination of the rate of hepatic secretion of bile. The amount of bile flowing into the gallbladder dropped dramatically after cannulation of the entire length of the intramural common duct, and rose sharply once the catheter was withdrawn. Gallbladder filling

also dropped precipitously after transection of the common duct, and rose steeply when the duct was clamped. However, surgical exteriorization of the entire intramural common duct and removal of all surrounding muscle tissue did not affect the rate of filling. Subsequent histologic examination of the denuded ducts confirmed that all muscular tissue had been removed. In a final experiment, the exteriorized common duct was transected in stages (2 mm at a time, beginning at the papilla), and gallbladder filling was measured after each of five successive cuts. After the initial 2 mm incision, the filling rate declined steadily as the intramural common bile duct was progressively eliminated. In all studies the rate of hepatic bile secretion remained constant. Based on these findings, the investigators concluded that gallbladder filling was dependent upon the occlusive ability of a structurally intact terminal common bile duct. However, since removal of all duodenal and sphincteric muscle tissue from an intact common duct did not reduce filling, Tansy *et al*. proposed that the occluding mechanism of the distal common duct was mediated by the vascular dynamics of the ductal epithelium, and not by action of the sphincter nor the duodenal musculature.

Cohn *et al*.[87] in 1979 performed transduodenal sphincteroplasty on six dogs, and studied them with cholecystokinin-cholecystography and bile analysis at five and ten weeks postoperatively. Intravenous cholangiography revealed gallbladder opacification on ten of twelve

occasions. One dog had no gallbladder visualization at five weeks, and another showed no filling at ten weeks. Contractility in response to CCK administration remained intact after sphincter ablation, although resting gallbladder volume was noted to be reduced, with mean values of 35.7 ml preoperatively, 28.1 ml at five weeks, and 18.8 ml at ten weeks. Alterations were also found in the composition of gallbladder bile. Cholesterol concentration did not change significantly, but diminished concentrations of both lecithin and bile acids resulted in a net increase in bile lithogenicity. Additionally, cultures of gallbladder bile revealed postoperative bacterial growth in all animals, as opposed to the finding of uniformly sterile bile before sphincteroplasty. Incompetence of the sphincter of Oddi was confirmed radiographically by the presence of duodenal-biliary reflux of contrast in all dogs, as well as the consistent finding of air in the common duct and gallbladder. The investigators concluded that gallbladder filling and contractility remained normal after sphincteroplasty, but that the resultant diminished concentrating ability, increased bile lithogenicity, and bacterial contamination represented a significant risk for gallbladder pathology.

In 1983 Rosseland and Kolmannskog[153] performed papillotomies on seven rabbits (using a standard papillotome and accessing the papilla through a duodenal incision), and analyzed gallbladder function with intravenous cholangio-

graphy after a three month follow-up period. Six control animals underwent duodenotomy and common duct cannulation, but no papillotomy was done. All thirteen animals showed normal gallbladder visualization preoperatively. Gallbladder filling did not occur after papillotomy in six of seven test animals, as compared to normal postoperative filling in all six control rabbits. Six months after papillotomy, radiographic contrast was instilled into a duodenal catheter. Free reflux of contrast material from the duodenum into the bile ducts occurred in six of seven test animals, confirming incompetence of the sphincter, whereas no reflux was evident in the six control rabbits. The results of this study clearly imply the importance of the sphincter of Oddi in gallbladder filling, at least in rabbits.

In 1984 Van der Linden and Kempi[154] studied a group of thirty normal subjects using computer-assisted ^{99m}Tc-HIDA cholescintigraphy. Quantitative analysis of isotope activity in specific regions of interest (ROI) yielded the following findings: 1) Visualization of the gallbladder tended to occur prior to that of the distal common bile duct. 2) The mean time after isotope injection at which gallbladder visualization became apparent was nearly identical in subjects with and without passage of activity into the duodenum. 3) Initial gallbladder filling occurred rapidly, as evidenced by a steep rise in the time-activity curve over the gallbladder ROI. This was typically preceded by an increase in activity in the proximal bile duct ROI, and

accompanied by a simultaneous plateau of bile duct activity.
4) On initial filling, activity rapidly reached the fundus
of the gallbladder, traveling along its long axis, and then
spread laterally. From these observations the authors
concluded that: 1) Closure of the sphincter of Oddi was not
required for gallbladder filling. 2) Filling occurs by a
gradual buildup of bile in the proximal ducts, followed by
abrupt entry into the gallbladder. 3) Initial flow of bile
into the gallbladder occurs by a forceful process. They thus
explained their results by proposing that gallbladder
filling is likely due to motor activity of the gallbladder
itself, and not dependent on biliary pressure generated by
the sphincter of Oddi.

In a discussion of this paper, however, Shreiner[155]
argued that the experimental findings did not justify the
authors' conclusion that the sphincter was not an important
component in the filling process. He emphasized that: 1)
"The fact that radioactivity appeared in the gallbladder at
the same time after injection, whether or not radioactivity
appeared in the duodenum, does not prove that the sphincter
of Oddi was not closed during the filling phase of the gall-
bladder," and 2) "Bile already present in the duct may
prevent radioactivity from reaching the region of the
[closed] sphincter before filling of the gallbladder." Van
der Linden and Kempi interpreted the observed abrupt (as
opposed to gradual) entry of bile into the gallbladder as
evidence that muscular action (rather than passive flow

under pressure) was responsible for gallbladder filling.
These two processes, however, are not necessarily mutually
exclusive. The authors themselves stated that "although very
informative on the flow of bile in the biliary tract, chole-
scintigraphy does not permit any conclusion as to the nature
of force responsible for that flow."[154] This filling pattern
could instead result from a steady buildup of pressure (due
to a closed sphincter) suddenly overcoming flow resistance
at the spiral valves of Heister.

Scott *et al.*[141] in 1985 measured gallbladder filling
indirectly in fasting dogs. Under steady state conditions
maintained by a continuous intravenous infusion of
[14]C-labelled taurocholic acid (TCA), the investigators used
a duodenal cannula to measure the rate of intestinal
delivery of labelled TCA. Since both the rates of hepatic
secretion and duodenal delivery of labelled bile acids could
be quantified, the fraction of secreted bile entering the
gallbladder could be calculated from the algebraic differ-
ence of these two measurements. This allowed determination
of the rate of gallbladder filling. In addition, implanted
bipolar electrodes recorded intestinal myoelectric activity.
Experiments were carried out first with the sphincter of
Oddi intact, and then with the common bile duct cannulated,
thereby eliminating any physiological effect of the
sphincter, and producing a constant resistance to bile flow.
Position of the papillary cannula was adjusted to simulate
different common duct pressures (+5, 0, and -20 cm H_2O), and

thus determine the effect of biliary flow resistance on duodenal bile delivery. In all experiments, fasting duodenal bile acid delivery (and thus gallbladder filling and emptying) showed regular periodic variations, in conjunction with the MMC. Cannulation of the common duct did not abolish gallbladder filling or alter this pattern. The calculated gallbladder filling rate, however, was found to be proportional to the experimentally induced biliary flow resistance. The results of this study thus suggest that filling of the gallbladder during fasting is affected by, but not dependent upon, biliary pressure. Whether common duct pressure is mediated by action of the sphincter or the duodenal musculature cannot be inferred from this study, since cannulation of the duct would interfere with either mechanism.

In 1988 Hutton et al.[86] investigated the spontaneous passage of glass beads from canine gallbladders as well as changes in gallbladder ejection fraction after papillotomy. Papillotomy was performed through a duodenal incision using a standard papillotome. Quantitative cholescintigraphy was used to measure gallbladder ejection fraction before and at least one month after papillotomy. In this technique, computer acquisition was begun upon intravenous injection of 3.0 mCi of ^{99m}Tc-PIPIDA, and intravenous cholecystokinin was administered once activity over the gallbladder reached a plateau. After gallbladder activity fell to a new constant level, ejection fraction was calculated from the difference

in counts between the two plateaus, divided by counts at the first plateau. Since the investigators were able to measure this parameter, gallbladder filling must have occurred, although no specific comment was made to this effect. In discussing observed decreases in gallbladder volume (both in the resting state and after stimulation with CCK) following papillotomy, Hutton *et al*. stated that "Although these reduced gallbladder volumes after sphincterotomy could be a result of impaired gallbladder filling, they seem more likely to be a result of improved emptying." The authors thus concluded that sphincter ablation produces a much more significant effect on gallbladder emptying than filling.

Historically, medical scientists believed the sphincter of Oddi directed the flow of bile into the gallbladder. Multiple studies, however, have proposed the action of other physiologic mechanisms in this process. Table 7 summarizes the implications of these various experiments on gallbladder filling. With experimental evidence suggesting both active and passive modes of gallbladder filling, it is likely that these two processes operate in conjunction. Although the terminal common bile duct appears to play some role in the filling process, it is not clear whether its occlusive action is mediated by muscular constriction (either sphincteric, duodenal, or both) or some other mechanism, as yet undetermined. This investigation was designed to ascertain the role of the sphincter of Oddi in gallbladder filling in humans, by analyzing bile flow scintigraphically

in patients with an intact gallbladder and an ablated sphincter. With the development and widespread use of endoscopic papillotomy, the number of individuals with this specific anatomic configuration has greatly increased. In such persons, a single variable--the sphincter of Oddi--has been eliminated, providing an excellent model for studying the effect of this structure on bile flow.

Table 7: Summary of experimental data on the mechanism of gallbladder filling.

Investigator(s)	Date	Animal	Exp Model	Findings	Passive SO	Duod	Active (GB)
Copher	1925	Dog	cannulate CBD	No GB vis (IVC)	+ or +		
Copher et al.	1926	Dog	rubber GB	"GB" vis (IVC)	+ or +		
Burget	1926	Dog	bypass SO, + drugs	Nl pressure Δ's	−	+	
Whitaker	1926	Dog	SO ablation	GB vis (IVC)	−		
		Cat	SO ablation	No GB vis (IVC)	+		
Jones & Smith	1952	Human	sphincteroplasty	No GB vis (OCG)	+		
Lempke	1960	Human	sphincterotomy	GB vis (OCG)	−		
Tansy et al.	1974	Dog	1) cannulate CBD	↓GB bile flow	+ or +		
			2) transect CBD	↓↓GB bile flow	+ or +		
			3) excise SO, duod	Nl GB bile flow	−	−	
Cohn et al.	1979	Dog	sphincteroplasty	1) GB vis (IVC)	−		
				2) ↓GB volume	?		
Rosseland	1983	Rabbit	papillotomy	No GB vis (IVC)	+		
Van der Linden	1984	Human	quant HIDA	1) GB vis before distal CBD	?		
				2) Abrupt GB filling			?
Scott et al.	1985	Dog	cannulate CBD, vary pressure	GB bile flow prop to pressure	?	?	?
Hutton et al.	1988	Dog	papillotomy	GB vis (PIPIDA)	−		

Column header group: **Concl re: GB Filling** (Passive: SO, Duod; Active: GB)

Abbreviations: **GB** = gallbladder; **CBD** = common bile duct; **SO** = sphincter of Oddi; **Duod** = duodenum; **IVC** = intravenous cholangiography; **OCG** = oral cholecystography; **vis** = visualization, **Nl** = normal, ↓ = decreased, Δ = change

Conclusions: The results of each study are interpreted as either supporting (+) or opposing (−) the different possible mechanisms of gallbladder filling. A **?** indicates that the experimental results suggest a particular conclusion, but offer no definitive support. Possible physiologic regulators controlling passive gallbladder filling include the sphincter of Oddi (SO) and the duodenal musculature (Duod).

Please refer to the text for a full description of these studies.

MATERIALS AND METHODS

Subjects:

Between June 3, 1987 and February 1, 1989, twelve patients with intact gallbladders underwent endoscopic papillotomy at Yale-New Haven Hospital. All of these individuals' personal physicians were contacted; the details of the study were explained, and permission to contact the patient was requested. Ten persons were contacted and invited to participate in the study. Two were lost to follow-up. Six people agreed to serve as experimental subjects. Of these, there were four females and two males, of ages 57, 66, 73, 77, 65, and 80, respectively.

This study was approved by the Human Investigation Committee of the Yale University School of Medicine, the Yale-New Haven Hospital Radioisotope Committee, and the Yale University Radioactive Drug Research Committee.

Experimental Protocol:

All subjects were instructed to fast for at least four hours (preferably overnight) prior to beginning the study. On the day of the study, subjects were asked if they had experienced any symptoms of biliary disease (abdominal pain, fever, nausea, vomiting, bloating, jaundice, dark urine, or light stool) since the time of papillotomy. After giving informed consent, each subject underwent computer-assisted

cholescintigraphy as described below. Between the initial and delayed views, abdominal ultrasonography was performed to examine the gallbladder and to look for biliary air. Following completion of the scintigraphic study, an upright abdominal radiograph and a coned-down view of the right upper quadrant were obtained, also for determining the presence of air in the biliary tract. Lastly, a limited barium upper GI examination was done, in order to verify incompetence of the sphincter of Oddi by demonstration of 1) reflux of contrast from the duodenum into the common bile duct, and 2) free drainage of refluxed barium. All studies were performed in the Yale-New Haven Hospital Diagnostic Imaging facility.

Endoscopic Papillotomy:

All papillotomies were performed by the same gastroenterologist, using an Olympus JFV-10 side-viewing endoscope, a Zimmon papillotome, and an Olympus UES Electro-surgical unit. Indications for papillotomy included choledocholithiasis in four patients (causing ascending cholangitis in one patient and gallstone pancreatitis in another), pancreatitis (possibly due to pancreatic divisum or sphincter of Oddi spasm) in one patient, and sphincter of Oddi stenosis in one patient.

Cholescintigraphy:

Scintigraphy was performed using 5.0 mCi (185 MBq) of ^{99m}Tc-DISIDA (disofenin), N,a-(2,6,-diisopropylacetanilide)-iminodiacetic acid (Hepatolite; New England Nuclear, North Billerica, Massachusetts), as the tracer. Images were obtained with a Siemens ZLC large field of view scintillation camera outfitted with a low-energy all-purpose (LEAP) parallel hole collimator. After an initial flow study, serial anterior 500,000 count scintigrams were obtained at five minute intervals for 45 minutes, with delayed views taken at one to four hours as needed. Additional left anterior oblique (LAO), right anterior oblique (RAO), and right lateral views were obtained between 45 and 60 minutes post-injection.

Quantification of cardiac and hepatic uptake and hepatic excretion was performed with a Picker 512-PCS computer, acquiring images in a 64 X 64 matrix. Regions of interest (ROI) were selected over the heart and liver. The liver ROI was positioned so as not to include bile ducts or gallbladder. Perfusion curves were generated by plotting the number of counts in each ROI over the first 120 seconds after injection of tracer (see Figures 16A, 22A, & 25A). Hepatic excretion curves were generated by plotting the number of counts within the liver ROI over the initial 45 minutes of the study. The half-time hepatic clearance was determined from the slope of the time-activity curve over

the liver ROI (see Figures 16B, 22B, & 25B), from the time of peak activity in this region until the end of the period of computer acquisition of data (45 minutes). The slope of the curve was calculated using a single exponent least-squares fit. The computer program automatically corrected for radioactive decay of the isotope. Normal range for half-time clearance is 16-24 minutes (based on data from 30 normal volunteers studied at Yale-New Haven Hospital during 1978-1980). All cholescintigraphic studies were reviewed by the attending nuclear medicine staff member.

Ultrasonography:

Real-time ultrasonography was performed using an ATL 600 ultrasound scanner, equipped with a 3 MHz sector-display transducer (Advanced Technology Laboratories, Seattle, Washington). Images of the liver, gallbladder, and common bile duct were obtained. Sonograms were taken in the supine, left lateral decubitus, and erect positions. The right and left lobes of the liver were scanned for the presence of air in the intrahepatic bile ducts. The finding of echogenic foci within the liver parenchyma, accompanied by "dirty" acoustic shadowing,[156] (see Figure 7) was considered evidence of intrabiliary air. All sonograms were performed by an ultrasound technologist and reviewed by a staff radiologist.

Upper GI Examination:

Fluoroscopy was performed following ingestion of barium sulfate. When possible, the following maneuvers were employed in order to maximize the probability of contrast flow into the common bile duct: 1) repeated turning of the subjects, 2) prone and Trendelenburg positioning (placing the papilla of Vater in a dependent position), and 3) abdominal compression. Multiple radiographs were taken as barium flowed through the duodenum. All films were reviewed by a gastrointestinal radiologist.

RESULTS

The gallbladder was seen on cholescintiscan in three (50%) of the six subjects. One subject (17%) demonstrated rapid excretion of tracer from the liver (half-time clearance of 11 minutes, as compared to the normal value of 16-24 minutes). Hepatic excretion was delayed (clearance half-time from 27-54 minutes) in the remaining five subjects (83%). Air in the biliary tract was noted in three subjects (50%) on both sonography and plain abdominal radiography. No air was seen on plain film or ultrasound in the other three subjects (50%). Barium examination revealed reflux of contrast from the duodenum into the common bile duct in two subjects (33%). Both subjects with demonstrable barium reflux had evidence of biliary air on plain film and ultrasonography, and one showed rapid clearance of tracer from the liver. One subject had evidence of biliary air on both plain film and ultrasound, but no observable reflux of barium. All six subjects reported that they had been completely free of biliary symptoms since papillotomy.

Thus, radiologic confirmation of sphincter of Oddi incompetence was obtained in only three subjects (50%). The remaining three subjects demonstrated no biliary air by plain film or sonography, no contrast reflux, and delayed hepatic clearance of tracer. Filling of the gallbladder on scintigraphy was seen in one (33%) of the three subjects with supportive evidence of a functionally ablated

sphincter. Visualization or nonvisualization of the gall-
bladder by cholescintigraphy did not correlate with any of
the other variables measured (estimated papillotomy incision
size, time since papillotomy, biliary air on plain film or
ultrasonography, contrast reflux into the common bile duct,
^{99m}Tc-DISIDA hepatic clearance half-time, and post-
papillotomy clinical history).

The results are summarized in table 8, and the
individual case histories and findings are described below.
Reference normal values for laboratory tests mentioned below
are as follows: alkaline phosphatase: 10-70 units/l, total
bilirubin: less than 1.50 mg/dl, direct bilirubin: less than
0.30 mg/dl, serum glutamic-oxaloacetic transaminase (SGOT):
15-35 units/l, serum glutamic-pyruvic transaminase (SGPT):
less than 32 units/l, amylase: 40-150 units/dl, lipase: less
than 1.5 units/ml, and white blood count (WBC): 4,000-10,000
cells/mm^3 .

Table 8: Results of ^{99m}Tc-DISIDA cholescintigraphy in post-papillotomy subjects.

Subj	Pap Size	Post-Pap Time	GB Vis	Air on XR	Air on US	CBD Reflux	Clear Half-Time	Post-Pap Sx
1	1 cm	4.5m	Yes	Yes	Yes	Yes	40 min.	No
2	1.5+ cm	4m	No	Yes	Yes	Yes	11 min.	No
3	1 cm	7.5m	Yes	No	No	No	54 min.	No
4	1.5 cm	1m	Yes*	No	No	No	27 min.	No
5	1 cm	21m	No*	No	No	No	31 min.	No
6	1.0 cm	2m	No*	Yes	Yes	No	44 min.	No

Abbreviations: **Subj** = subject number, **Pap Size** = estimated length of papillotomy incision; **Post-Pap Time** = Time since papillotomy (in months); **GB vis** = visualization of the gallbladder by cholescintigraphy; **Air on XR** = biliary air noted on abdominal plain film; **Air on US** = biliary air detected by ultrasonography; **CBD Reflux** = reflux of barium from the duodenum into the common bile duct on upper GI exam; **Clear Half-Time** = calculated half-time for clearance of radiopharmaceutical from the liver ROI (normal = 16-24 min.); **Post-Pap Sx** = persistence of the subjects' original presenting symptoms (as described in the individual case histories), or other complaints attributable to the biliary system (RUQ pain, fever, nausea, vomiting, jaundice, dark urine, acholic stools) following endoscopic papillotomy.

*These subjects demonstrated gallbladder visualization on a previous cholescintiscan. Prior scans were performed two weeks before papillotomy in subject #4, six years before papillotomy in subject #5, and two days before papillotomy in subject #6.

Case 1: An 80 year old male presented to Yale-New Haven Hospital on Sept. 14, 1988, with complaints of right upper quadrant abdominal pain, nausea and vomiting, and fever (101.8°F). He was not jaundiced, and had noted no change in urine or stool color. He had been hospitalized for right upper quadrant pain and jaundice on three previous occasions in the last eleven years. Gallstones were documented by ultrasound in the past. Past medical history was notable for a subtotal gastrectomy with Bilroth II anastomosis, an old anterior wall MI, exertional angina, and three CVA's, the most recent one occurring one week before admission. Admission labs included: WBC 15,600 cells/mm³, alkaline phosphatase 269 units/l, total bilirubin 1.8 mg/dl (direct 0.6 mg/dl), SGOT 519 units/l, amylase 52 units/dl, and lipase 0.3 units/ml. The patient was diagnosed as having ascending cholangitis, likely secondary to an obstructing common duct stone, and was treated initially with hydration and antibiotics. He remained febrile, developed dark urine and acholic stools, and serum total bilirubin increased to 4.4 mg/dl (direct 2.7 mg/dl). Due to the increased risk of surgery following a recent CVA, the patient was referred for endoscopic papillotomy on Sept. 16, 1988. ERCP demonstrated a non-dilated biliary tree with a single common duct stone and several stones in the gallbladder (see Figure 6). A 1 cm incision was made and the stone was crushed and removed with a Dormia basket. The patient defervesced following stone extraction, and was discharged three days later.

Subject #1 participated in the research protocol on Feb. 1, 1989 (4.5 months after papillotomy). Since the papillotomy he had experienced no symptoms of biliary disease. The gallbladder visualized on cholescintigraphy (see Figure 7), first appearing at 20 minutes post-injection. The study was carried out to 3.75 hours, at which time the isotope had fully cleared from the liver. Hepatic excretion was delayed, with a half-time clearance of 40 minutes. Sonography demon-strated both stones and air in the gallbladder and air in the intrahepatic bile ducts (see Figure 8). Abdominal plain film showed air in the biliary tree (see Figure 9). Reflux of barium from the duodenum into the common bile duct was noted on upper GI exam (see Figure 10). The contrast drained immediately from the biliary system, since the duct was not evident on a repeat radio-graph taken less than one minute later.
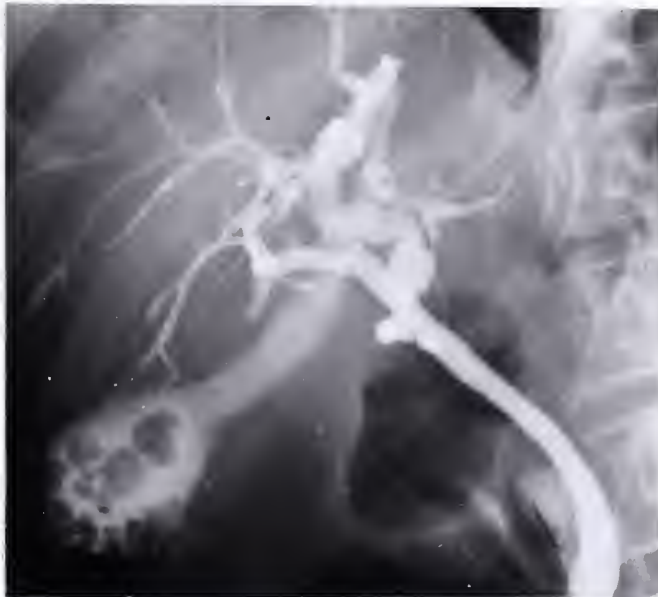
Figure 6: Subject #1: ERCP film showing filling
of the cystic duct and gallbladder with
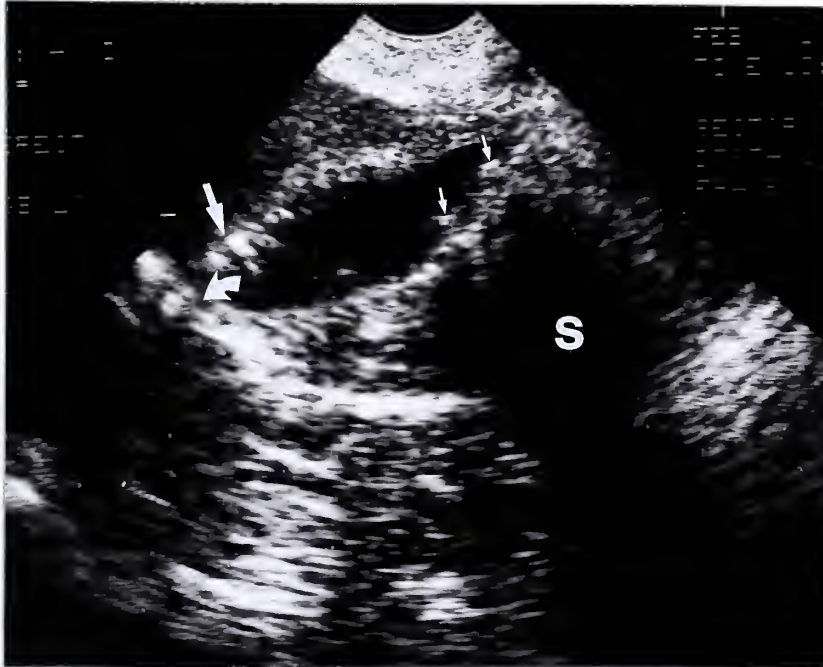contrast. The gallbladder contains numerous
gallstones.

(A)
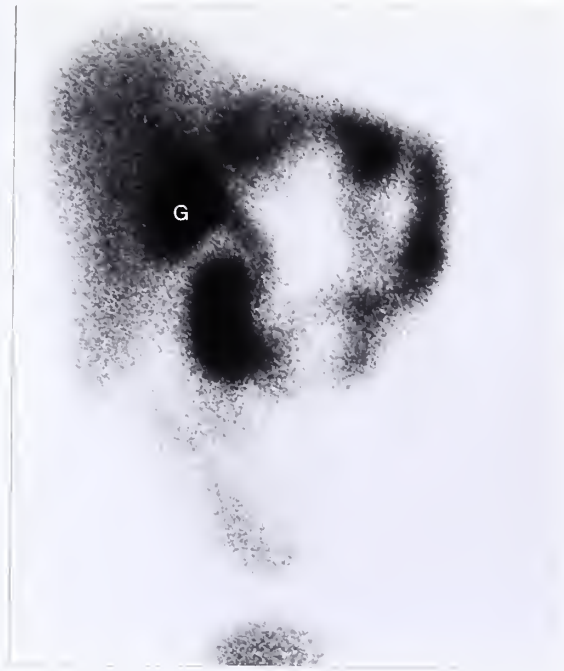
(B)

Figure 7: Subject #1: ^{99m}Tc-DISIDA cholescintigraphic images showing: (A) activity in the liver, gallbladder (G), and bowel at 45 minutes; and (B) activity in the gallbladder (g) and bowel, with nearly complete clearance of tracer from the liver, at 2 hours.
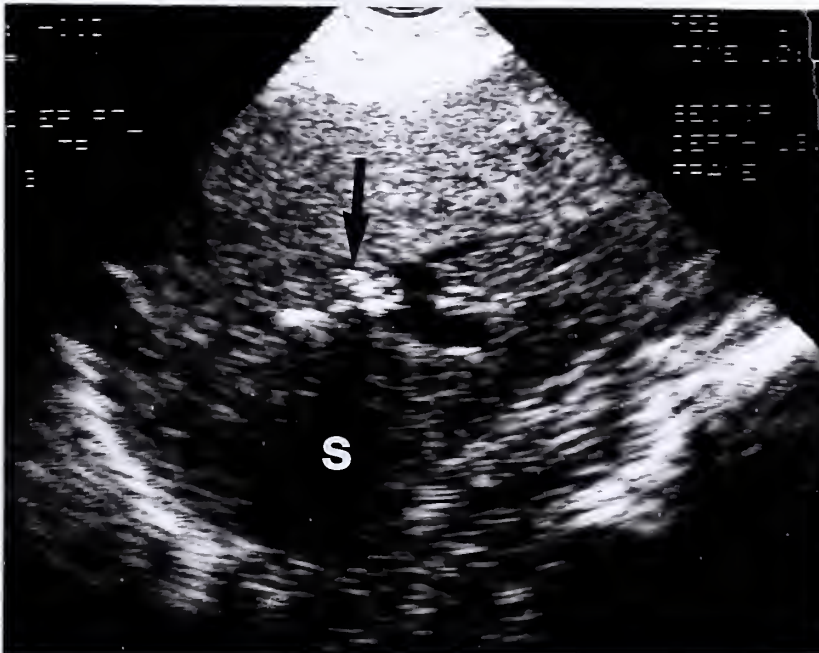
Figure 8: Subject #1: Ultrasound images of: (A) the gallbladder, containing gallstones [echogenic foci (small arrows) with complete acoustic shadowing (S)] in the dependent portion, and air [echogenic foci (large straight arrow) with "dirty" shadowing (curved arrow)] in the non-dependent portion; and (B) the liver, with air in the intra-hepatic bile ducts [echogenic foci (arrow) with shadowing (S)].

Figure 9: Subject #1: Plain abdominal film showing air in the biliary tract (arrows).

(A)

(B)

Figure 10: Subject #1:
(A) Film demonstrating
reflux of barium from the
duodenum into the common
bile duct (straight arrow)
on upper GI exam. Note also
the presence of air in the
proximal biliary tree
(curved arrow). This subject
had undergone a subtotal
gastrectomy with Bilroth II
anastomosis. (B) Detailed
view of the biliary tract
(showing air and contrast
reflux).

Case 2: A 66 year old female was admitted on Sept. 15, 1988, complaining of six weeks of intermittent upper abdominal pain, pruritis, jaundice, dark urine, and light stools. She had a history of morbid obesity, non-insulin dependent diabetes mellitus, and hypertension. She was afebrile, and had icteric sclerae. Labs on admission were remarkable for: total bilirubin 19.7 mg/dl (direct 11.2 mg/dl), SGOT 163 units/l, and alkaline phosphatase 264 units/l. Calcified gallstones, including one stone in the region of the cystic duct (see Figure 12), were noted on a plain abdominal film. Ultrasonography revealed a small gall-bladder with multiple stones, a dilated common bile duct measuring 10 mm (normal 6mm or less[87]), and normal caliber intrahepatic ducts. CT scan also showed a small gallbladder with stones, and stones in the common hepatic and common bile ducts (see Figure 11). The patient was diagnosed as having obstructive jaundice secondary to choledocholith-iasis. Endoscopic papillotomy was opted for because her extreme obesity represented a contraindication to surgery. ERCP on Sept 19, 1988 demonstrated a mildly dilated common hepatic duct, with two ductal stones (see Figure 12). The cystic duct and gallbladder did not visualize with contrast. A 1.5 cm papillotomy was made, but attempts at stone extrac-tion were unsuccessful. An internal stent was placed to maintain drainage (see Figure 13). The patient improved clinically and was discharged two days later. She was readmitted on Oct. 9, 1988, for a repeat ERCP and stone

extraction. ERCP on Oct. 11, 1988 revealed multiple common duct stones and biliary air, and filling of the cystic duct (see Figure 14). The papillotomy was extended and the stent removed. Only one stone could be extracted. Subsequently the patient experienced several bouts of right upper quadrant pain accompanied by transient elevations of liver function tests. This was presumed to be due to passage of stones. Serial abdominal plain films revealed that some of the gallstones had indeed passed. The patient improved and was discharged on Oct. 19, 1988.

Subject #2 participated in the research protocol on Feb. 8, 1989 (four months after papillotomy). Since the papillotomy she had had no symptoms of biliary disease. The gallbladder did not visualize on cholescintigraphy (see Figure 15). The study was carried out to two hours, at which time the liver activity had completely cleared. Hepatic clearance was rapid, with a half-time of 11 minutes (see Figure 16). Sonography revealed a small gallbladder containing stones (see Figure 17A), and air in the intra-hepatic bile ducts (see Figure 17B). Plain film demonstrated air in the biliary tree (see Figure 18). Reflux of barium from the duodenum into the common bile duct was noted on upper GI exam (see Figure 19). The contrast drained immediately from the biliary system.
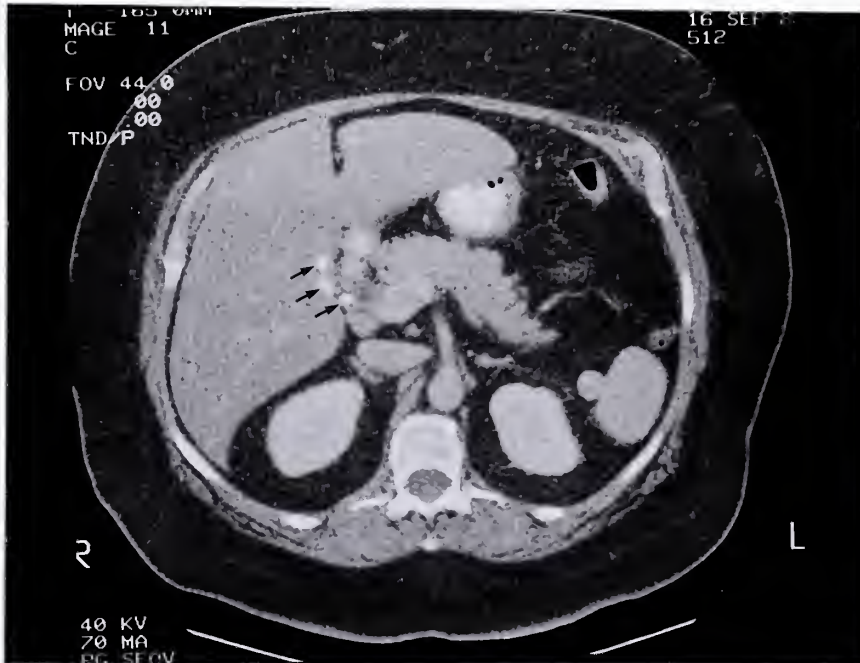
Figure 11: Subject #2: CT scan showing (A) calcified stones (arrows) in the common hepatic duct; and (B) a small gallbladder (curved arrow) containing a stone, and a calcified stone (straight arrow) in the intra-pancreatic portion of the common bile duct.

Figure 12: Subject #2: Pre-papillotomy ERCP film showing two stones (arrows) in the common duct, and no filling of the gallbladder with contrast.


Figure 13: Subject #2: Post-papillotomy abdominal film showing an internal biliary stent (open arrow), calcified stones in the common duct, a stone in the region of the cystic duct (straight arrow), and stones in the gallbladder (curved arrow).

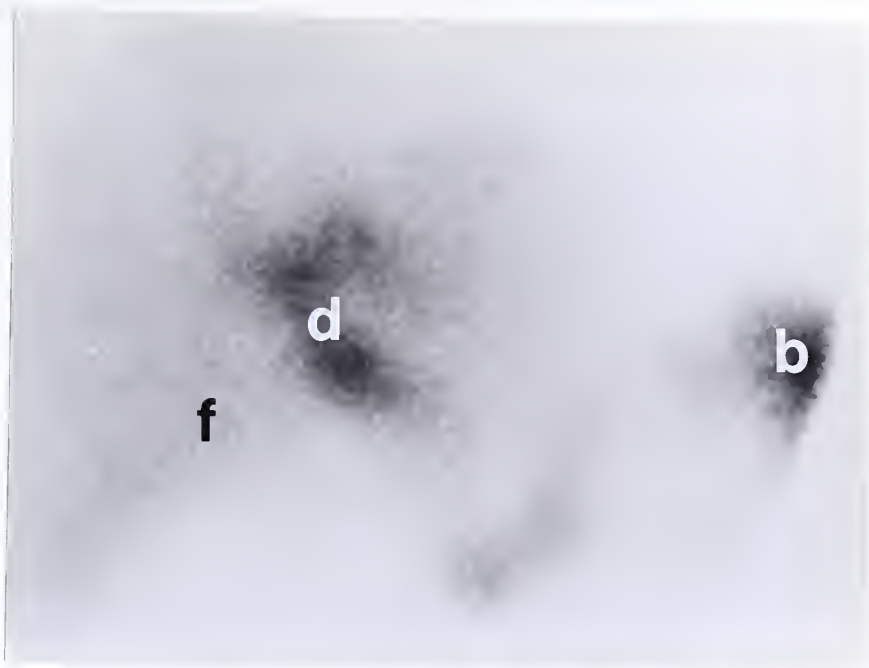**Figure 14:** Subject #2: Repeat ERCP films (one month after papillotomy) demonstrating:

(A) Multiple stones in the common duct and air (arrow) in the intra-hepatic bile ducts.
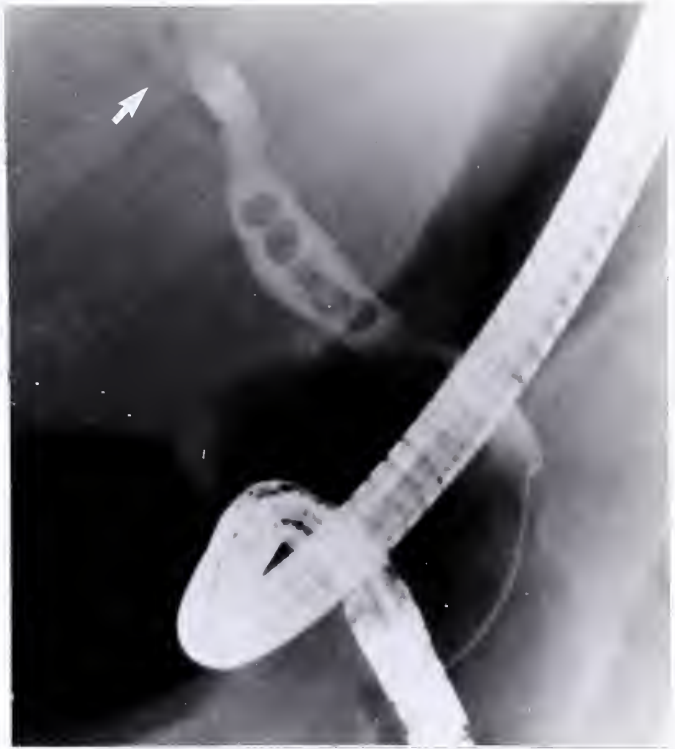
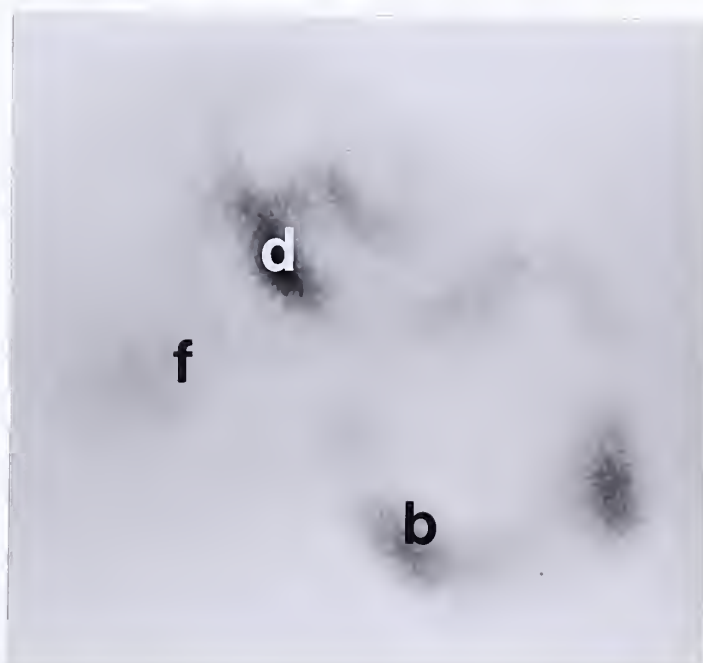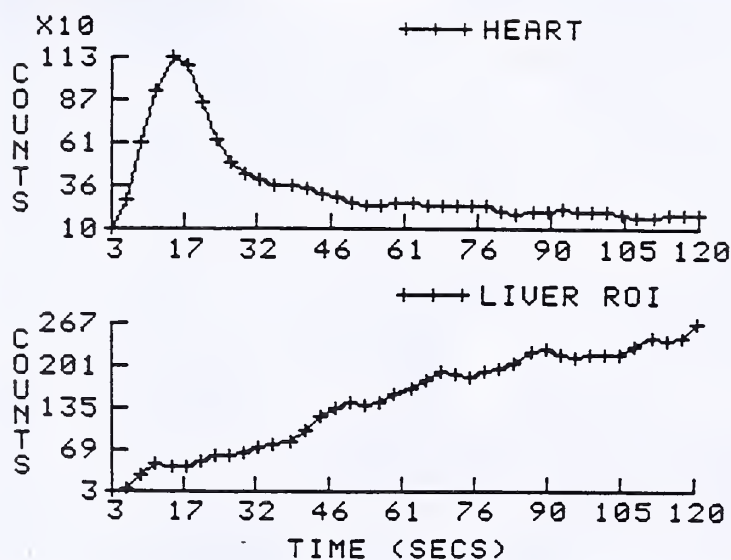(B) filling of the cystic duct with contrast (curved arrows).

(A)

(B)

Figure 15: Subject #2: ^{99m}Tc-DISIDA scan at (A) 40 minutes, showing tracer in the liver, bile ducts (d), and bowel (b), with no activity in the gallbladder fossa (f). (B) On 1 hour image (RAO view), most of the liver activity has cleared, tracer remains in the bile ducts (d) and bowel (b), but the gallbladder has not visualized (f).
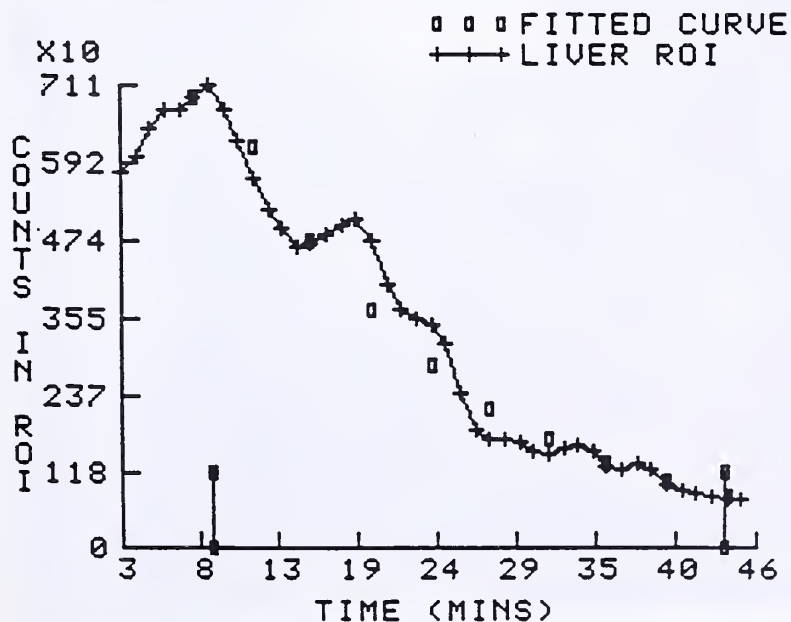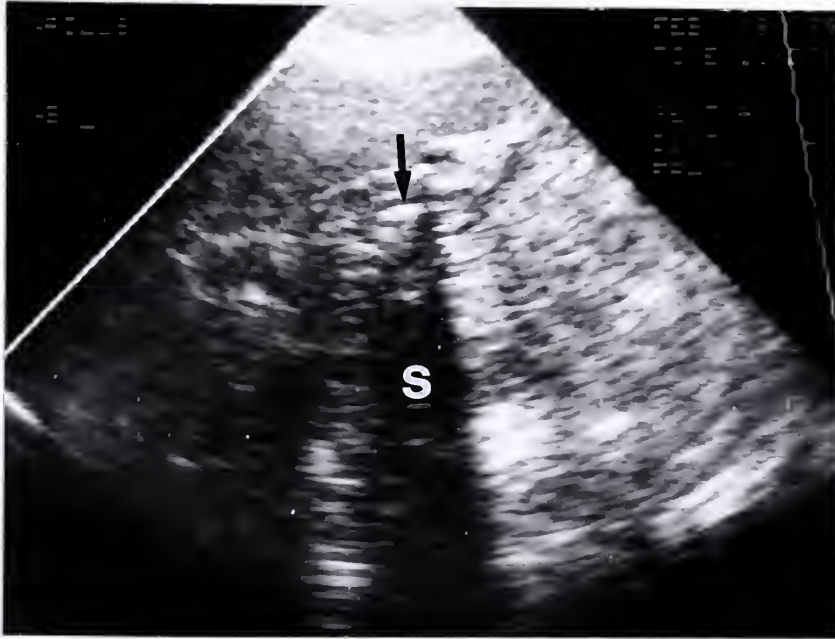
(A)

(B)

Figure 16: Subject #2: (A) ^{99m}Tc-DISIDA perfusion curves showing the bolus of tracer in the cardiac blood pool, and uptake of isotope by the liver. (B) Hepatic excretion curve demonstrating rapid clearance of tracer from the liver. The bars on the x-axis delineate the portion of the curve used to calculate the clearance half-time.
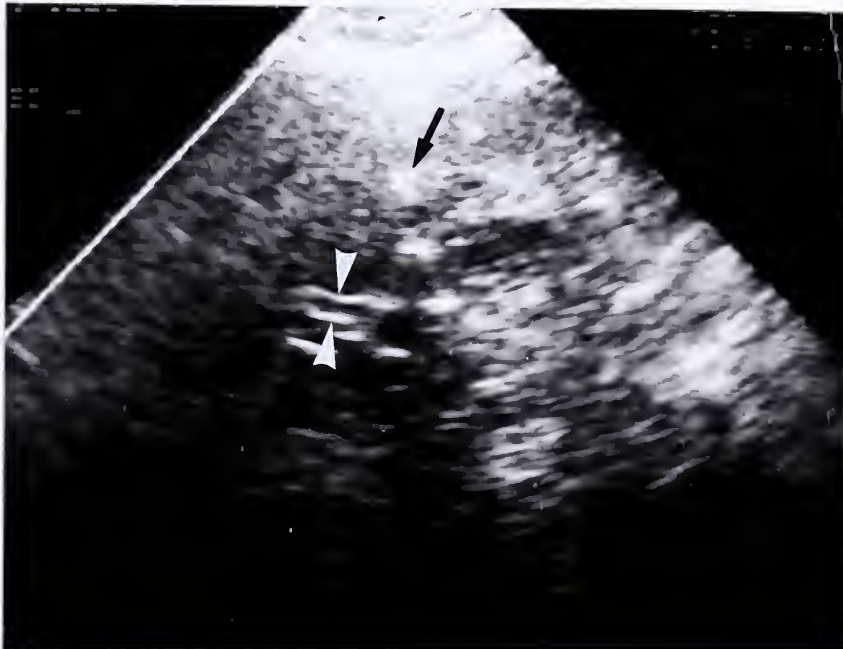
Figure 17: Subject #2: Ultrasound images showing (A) a small contracted gallbladder containing stones [echogenic focus (arrow) with prominent acoustic shadowing (S)]; and (B) a normal common bile duct (arrowheads), and air in the intrahepatic ducts (arrow).

Figure 18: Subject #2: Abdominal plain film showing a single stone in the gallbladder (curved arrow) and air in the biliary tree (straight arrows).

Figure 19: Subject #2: Upper GI exam demonstrating reflux of contrast from the duodenum into the common bile duct (arrows).

Case 3: A 57 year old female was admitted on June 28, 1988, complaining of multiple bouts of upper abdominal pain over the past year. She had not experienced jaundice, nausea, vomiting, bloating, change in urine or stool color, or fever. She had a history of several episodes of abdominal pain and chronically elevated transaminases and amylase (which had recently returned to normal). A previous gall-bladder ultrasound, abdominal CT scan, and oral cholecysto-gram were all normal. Admission labs included: alkaline phosphatase 55 units/l, total bilirubin 0.86 mg/dl (direct 0.11 mg/dl), SGOT 37 units/l, SGPT 80 units/l, and amylase 169 units/dl. She was given a presumptive diagnosis of sphincter of Oddi spasm, and was referred for ERCP and papillotomy. ERCP on June 28, 1988 revealed normal bile ducts and gallbladder (see Figure 20), and a pancreas divisum. A 1 cm papillotomy was made, through which an 8 mm balloon was passed. The patient developed post-ERCP pancreatitis on the following day, with amylase rising to 1900 units/dl and lipase increasing to 330 units/ml. This resolved with medical treatment, and she was discharged on July 5, 1988.

Subject #3 participated in the research protocol on Feb. 16, 1989 (7.5 months after papillotomy). Since her last hospitalization she had not experienced symptoms of biliary or pancreatic disease. The gallbladder visualized on cholescintiscan at 20 minutes (see Figure 21). Hepatic

excretion was delayed, with a half-time clearance of 54 minutes (see Figure 22). Sonography revealed a normal gallbladder, common bile duct, and liver, with no evidence of biliary air. No air was noted on plain film, and barium study showed no reflux into the common bile duct. Liver function tests ordered by her personal physician on the following day were all within normal limits (SGOT 27 units/l, alkaline phosphatase 62 units/l, total bilirubin 0.4 mg/dl).

Figure 20: Subject #3: ERCP film demonstrating
a normal biliary system and filling of the
cystic duct and gallbladder with contrast.
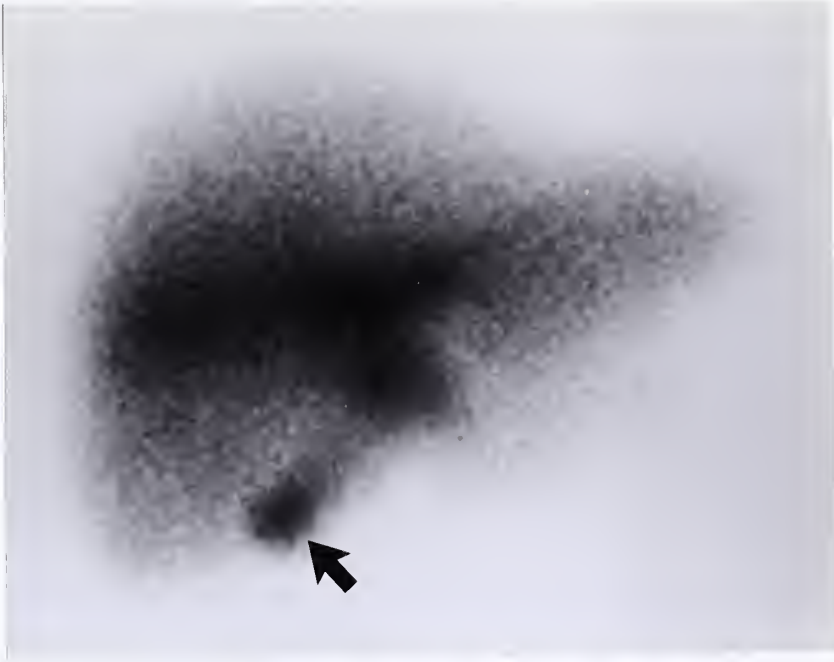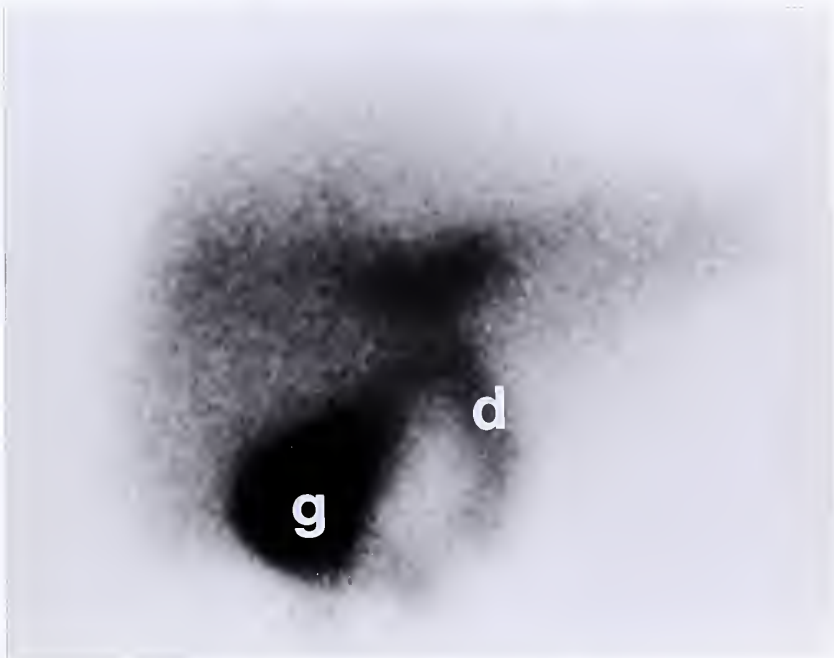
Figure 21: Subject #3: ^{99m}Tc-DISIDA scan showing (A) activity in the gallbladder (arrow) at 20 minutes; (B) visualization of the gallbladder (g) and bile ducts (d) at 45 minutes; and (C) clearance of isotope from the liver, with tracer remaining in the gallbladder (g) and bowel (b) at 90 minutes. (Figure continues on next page.)

(C)
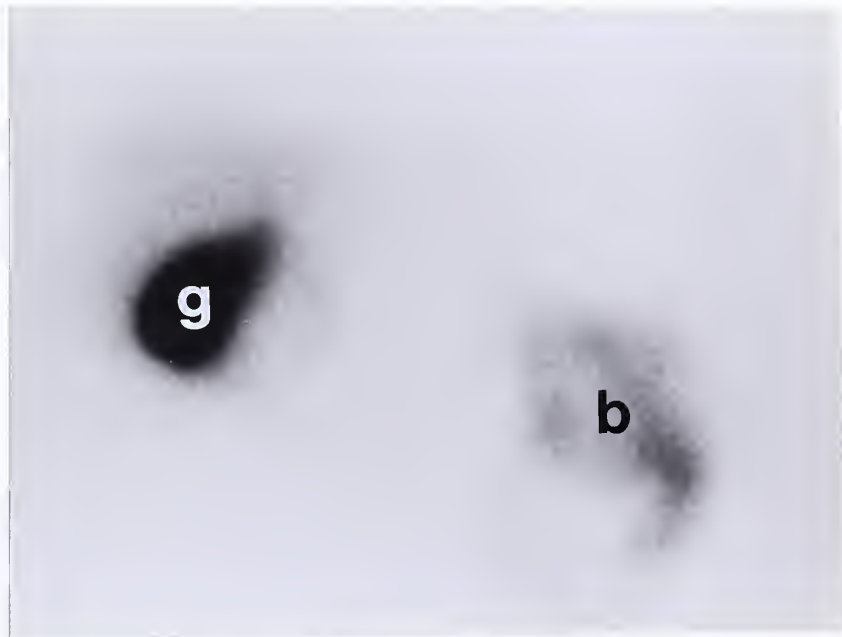
Figure 21: (cont.) Subject #3: (C) Delayed (90 minute) cholescintigraphic image, showing tracer in the gallbladder (g) and bowel (b).
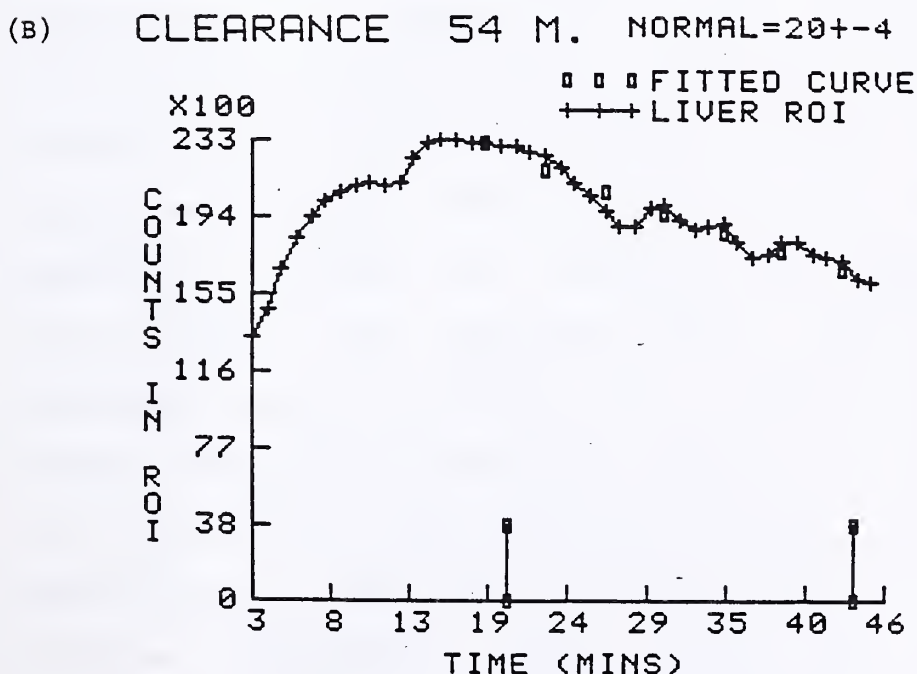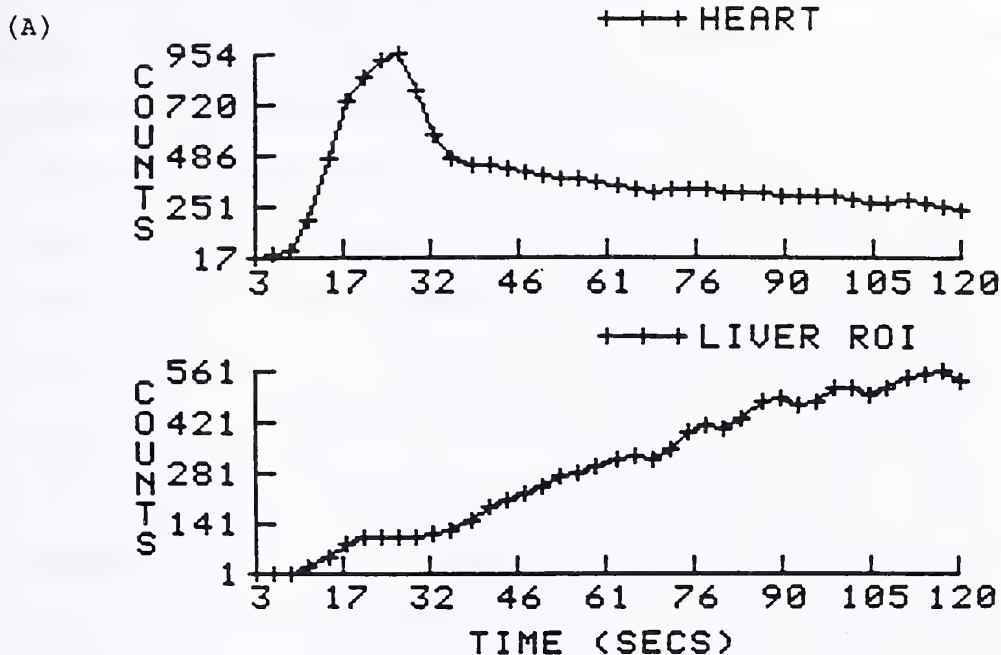
Figure 22: Subject #3: (A) ^{99m}Tc-DISIDA perfusion curves showing the bolus of tracer in the cardiac blood pool, and uptake of isotope by the liver. (B) Hepatic excretion curve demonstrating markedly delayed clearance of tracer from the liver. The bars on the x-axis delineate the portion of the curve used to calculate the clearance half-time.

Case 4: A 77 year old female was admitted on Jan. 31, 1989, complaining of several episodes of postprandial abdominal pain and nausea over the past six to eight months. She had no complaints of jaundice, dark urine, or light stools. Mild elevations of amylase and lipase were noted during one previous episode of right upper quadrant pain. A prior ultrasound showed a distended gallbladder with no stones, and a dilated common bile duct measuring 9.5 mm (normal 6 mm or less[87]) which increased to 11.5 mm following a fatty meal. The intrahepatic ducts were not dilated. A previous cholescintiscan (see Figure 23) visualized the gallbladder at 30 minutes. Hepatic uptake and excretion were normal (half-time clearance 23 minutes), but appearance of tracer in the bowel was delayed (absent at 45 minutes, but present at 90 minutes), suggestive of bile stasis in the common duct. A prior ERCP had also been attempted. The pancreatic duct did not opacify upon cannulation of the major papilla, but visualized after cannulation of the accessory papilla (evidence of a pancreas divisum). The patient was given a diagnosis of sphincter of Oddi stenosis, and referred for ERCP and papillotomy. Additional past medical history was notable for hypertension, mitral valve prolapse, degenerative joint disease, and several minor surgeries. Laboratory studies on admission included: total bilirubin 0.31 mg/dl (direct 0.03 mg/dl), SGOT 19 units/l, amylase 94 units/dl, lipase 0.2 units/ml, and WBC 6,700 cells/mm^3. ERCP on Feb. 1, 1989 demonstrated a mildly

dilated common bile duct (see Figure 24), and no filling of the pancreatic duct. No stones were seen. Papillotomy was begun with a precut papillotome, and the incision was extended to 1.5 cm after threading the cannula over a guide-wire. The patient did well after the procedure and was discharged on the following day.

Subject #4 participated in the research study on Mar. 3, 1989 (one month after papillotomy). Since that time she had been completely free of biliary symptoms. Cholescintigraphic findings were nearly identical to those of her pre-papillotomy scan. The gallbladder visualized at 15 minutes. Hepatic uptake was normal, and excretion was borderline delayed, with a half-time clearance of 27 minutes (see Figure 25). Excretion from the common duct was also delayed. No bowel activity was present at 45 minutes (see Figure 26A), but a delayed view (2 hr) demonstrated complete clearance of the liver and visualization of the bowel (see Figure 26B). No biliary air was evident on plain film or ultrasound, and reflux of barium into the common duct did not occur. Ultrasound revealed a dilated common bile duct measuring 8 mm (see Figure 27).

Figure 23: Subject #4: Pre-papillotomy ^{99m}Tc-DISIDA scan showing (A) tracer in the liver, common duct (d), and gallbladder (g) at 35 minutes; and (B) activity in the gallbladder (g) and bowel (b) at 90 minutes.

Figure 24: Subject #4: ERCP film showing a
dilated common hepatic duct (d) and filling of
the gallbladder with contrast. The finding of
a dilated common duct and delayed drainage of
contrast from the biliary tree, in the absence
of an obstructing lesion, is consistent with
sphincter of Oddi stenosis.
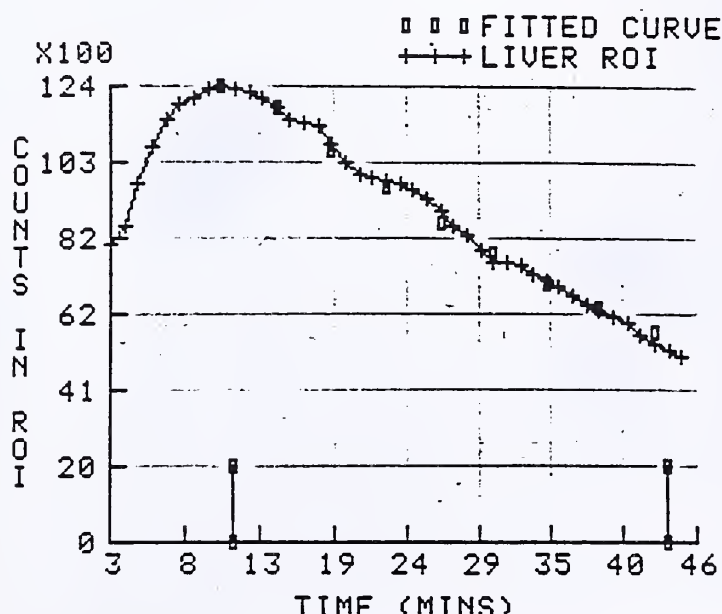
Figure 25: Subject #4: (A) ^{99m}Tc-DISIDA perfusion curves showing the bolus of tracer in the cardiac blood pool, and uptake of isotope by the liver. (B) Hepatic excretion curve demonstrating mildly delayed clearance of tracer from the liver. The bars on the x-axis delineate the portion of the curve used to calculate the clearance half-time.

(A)

(B)
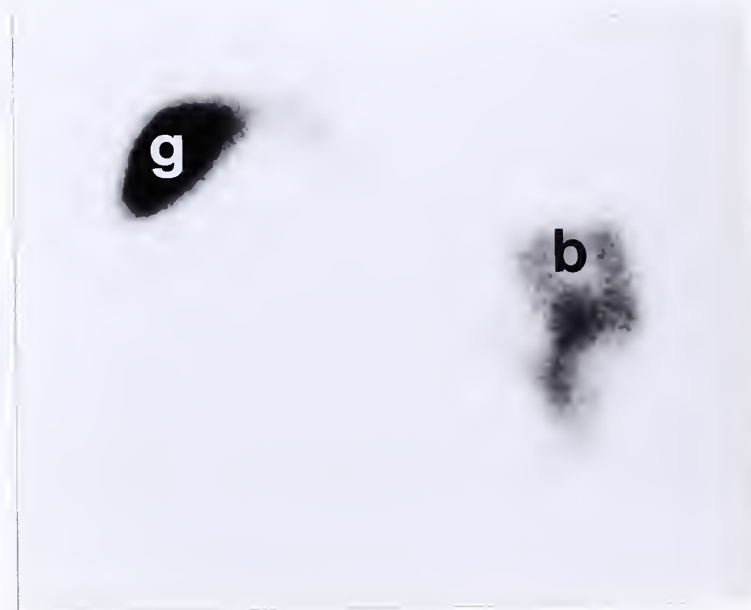
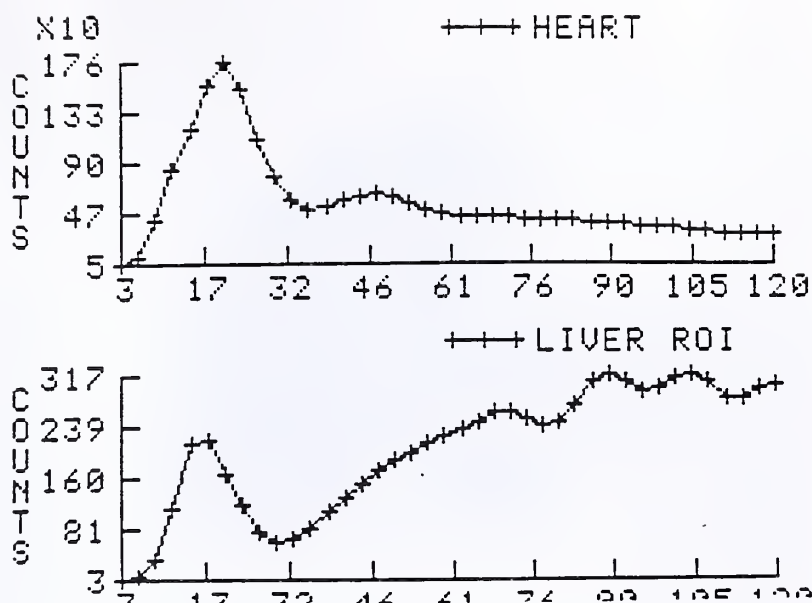**Figure 26:** Subject #4: Post-papillotomy ^{99m}Tc-DISIDA scan showing: (A) activity in the liver, common duct (d), and gallbladder (g) at 35 minutes; and (B) tracer in the gallbladder (g) and bowel (b) at 2 hours.
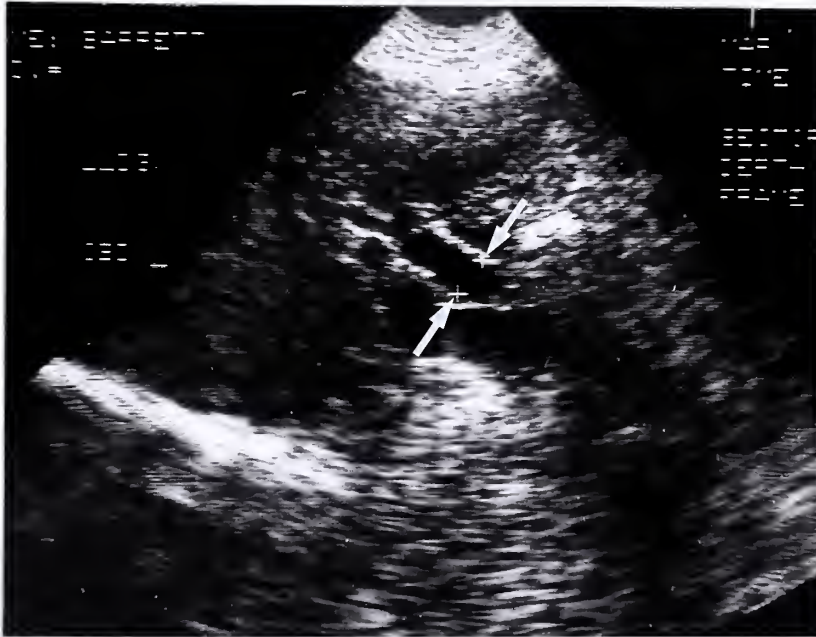
Figure 27: Subject #4: Ultrasound image demonstrating a dilated common bile duct measuring 8 mm (normal = 6 mm or less). Arrows point to cursors used to measure duct diameter.

Case 5: A 72 year old female presented with fever (103°F), right upper quadrant pain, nausea, and vomiting, on May 29, 1987. She was not jaundiced and had no change in urine or stool color. She had experienced a similar episode earlier that month, which resolved on antibiotics. Ultrasound at that time did not demonstrate gallstones. Cholescintiscan (see Figure 28) showed a high grade common duct obstruction, with no visualization of the ducts, gallbladder, or bowel at four hour delay (non-diagnostic for acute cholecystitis). The patient had also undergone cholescintigraphy in 1981 (see Figure 29), which demonstrated a normal gallbladder first visualized at 25 minutes. Past medical history was notable for morbid obesity (370 lbs), hypertension, asthma, and non-insulin dependent diabetes mellitus. Admission labs included: amylase 816 units/dl, lipase 5.2 units/ml, alkaline phosphatase 120 units/l, SGOT 52 units/l, total bilirubin 1.02 mg/dl (direct 0.54 mg/dl), and WBC 7,300 cells/mm^3. She was thought to have cholangitis and gallstone pancreatitis. She was judged to be an unacceptable risk for general anesthesia because of her asthma and obesity, and was thus referred for ERCP and possible papillotomy. ERCP on June 3, 1987 revealed a stone in the common bile duct and several stones in the gallbladder (see Figure 30). A 1 cm papillotomy was made, and the ductal stone was extracted. She improved clinically and was discharged after two days. Nine months later she successfully underwent a total abdominal hysterectomy and

bilateral salpingo-oophorectomy for endometrial carcinoma, and has since recovered.

Subject #5 participated in the study on Mar. 14, 1989 (21 months after papillotomy). She denied any interim biliary symptoms. The gallbladder did not visualize on cholescintiscan (see Figure 31). The study was carried out to 2.25 hours, by which time liver activity had completely cleared. Nonvisualization of the gallbladder was confirmed by placing a radioactive marker on the skin over the position of the gallbladder (as determined by sonography). Hepatic uptake was normal, and excretion was delayed, with a half-time clearance of 31 min. Ultrasound revealed a thickened gallbladder wall (see Figure 32) measuring 6 mm (normal wall thickness is 2 mm or less[87]), and no biliary air. No air in the biliary tract was seen on plain abdominal film. Reflux of barium into the common duct did not occur. Of note, the contrast study in this subject could not be performed under optimal conditions, since her large size inhibited her mobility and prevented her from lying prone.

Figure 28: Subject #5: ^{99m}Tc-DISIDA scan (delayed four hour image) performed one month before papillotomy (1987) showing activity only in the liver, with no visualization of the common duct, gallbladder, or bowel. This finding is consistent with complete biliary obstruction, and is non-diagnostic for acute cholecystitis.
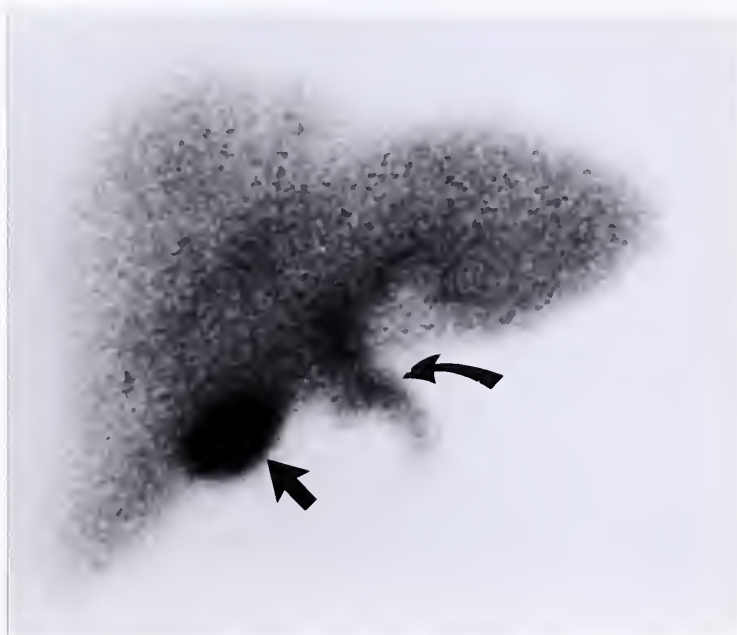
Figure 29: Subject #5: ^{99m}Tc-DISIDA scan from 1981 (six years before papillotomy), showing visualization of the gallbladder (straight arrow) and common duct (curved arrow).
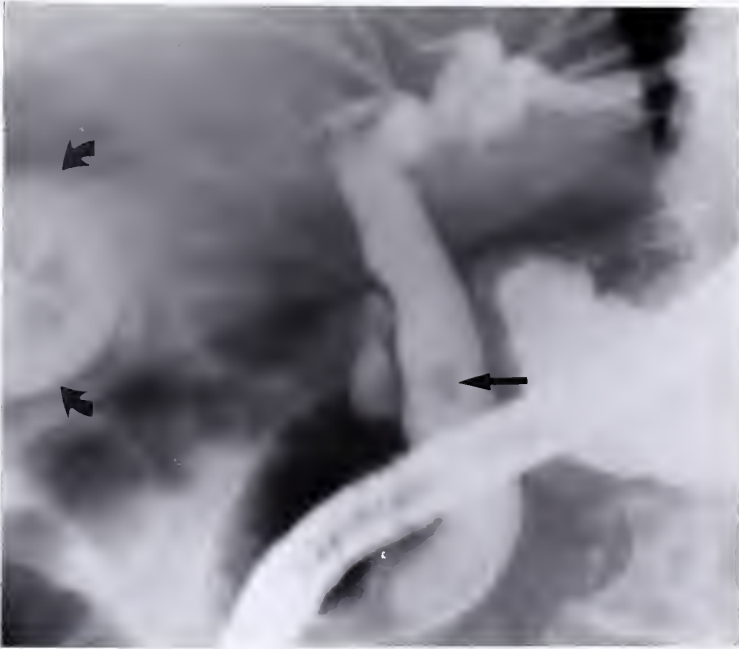
Figure 30: Subject #5: ERCP film showing a stone
(straight arrow) in the common bile duct and a
contrast-filled gallbladder (curved arrows)
containing multiple faceted gallstones.

Figure 31: Subject #5: Post-papillotomy ^{99m}Tc-HIDA scan (2 hr image) showing tracer in the bowel (b), and no visualization of the gallbladder. A radioactive marker (arrow) was placed over the position of the gallbladder, as determined by ultrasound.
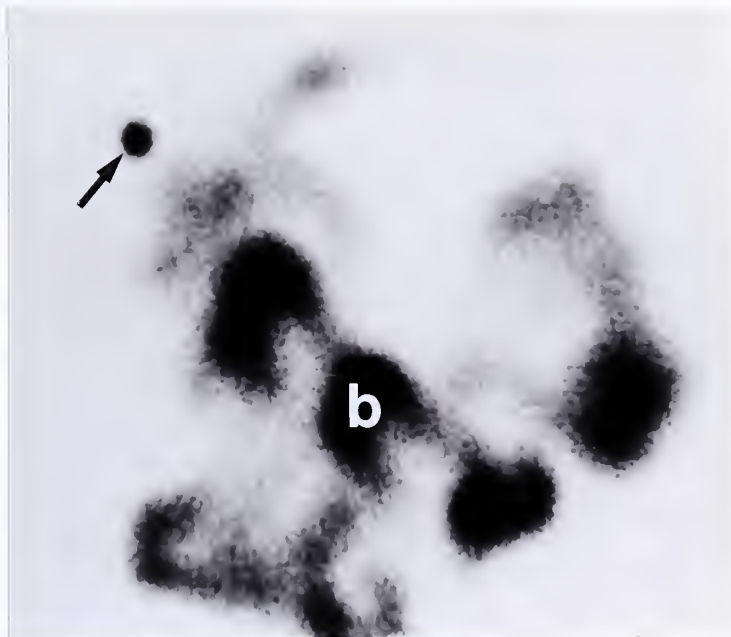
Figure 32: Subject #5: Ultrasound of the gallbladder, showing a thickened wall, measuring 6 mm (normal = 2 mm or less). Arrow points to cursors used to measure wall thickness.
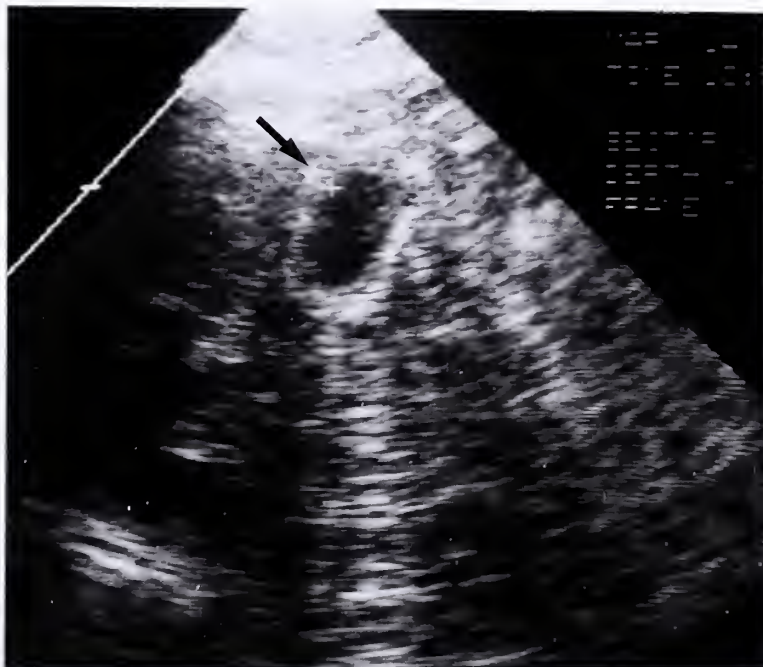
Case 6: A 65 year old male was admitted on Jan. 18, 1989, complaining of sharp mid-epigastric pain over the last four days, accompanied by mild fever. The patient had experienced several episodes of similar pain over the past 20 years. He noted no nausea, vomiting, jaundice, dark urine, or acholic stools. The patient was anicteric and afebrile. Past medical history was notable for a Schatzke ring and benign prostatic hypertrophy. The patient was initially seen at another hospital. An ultrasound revealed a dilated common bile duct and possible hydrops of the gall-bladder. No stones were seen. A cholescintiscan showed no excretion from the liver at two hours. On delayed (19 hour) view the gallbladder and bowel were visualized. The patient then came to Yale-New Haven Hospital for further work-up and treatment. Laboratory studies on admission revealed alkaline phosphatase 434 units/l, total bilirubin 0.82 mg/dl (direct 0.16 mg/dl), SGOT 197 units/l, SGPT 400 units/l, amylase 95 units/dl, lipase 0.6 units/ml, and WBC 6,000 cells/mm^3. An ERCP was performed on Jan. 19, 1989. Cholangiogram revealed a single filling defect in the distal common bile duct, and several filling defects in the right and left hepatic ducts. The common duct was not dilated. The cystic duct and gall-bladder filled with contrast, and no stones were seen in the gallbladder. A 1.0 cm papillotomy was performed, after which a single small stone passed spontaneously through the papilla. The patient developed post-ERCP pancreatitis on the following day, with an amylase of 3240 units/dl and lipase

65.0 units/ml. He recovered over the next few days, and was discharged on Jan. 24, 1989.

Subject #6 participated in the study on Mar. 31, 1989 (two months after papillotomy). Since the papillotomy he had experienced no biliary symptoms. The gallbladder was not seen on scintigraphy. By two hours post-injection nearly all tracer had cleared the liver. Delayed anterior and right lateral views showed an anterior area of concentrated activity in the region of the gallbladder. However, this activity cleared after the subject drank a glass of water, and thus was demonstrated to be due to pooling of tracer within a loop of bowel. Hepatic clearance half-time was 44 minutes (delayed). Ultrasound revealed air in the intra-hepatic bile ducts. No stones were seen in the gallbladder. Air in the biliary tree was also seen on plain film. No reflux into the common bile duct was noted on upper GI exam. Liver function tests drawn on the day of the study were all within normal limits: alkaline phosphatase 96 units/l, total bilirubin 0.98 mg/dl (direct 0.22 mg/dl), SGOT 38 units/l, and SGPT 40 units/l.

DISCUSSION

It is difficult to draw definitive conclusions from the results of this investigation, because of the small number of subjects involved. This is related to the specific population studied. Although an increasing percentage of individuals with an intact gallbladder are being treated with endoscopic papillotomy, the number of such persons seen at any one institution is not large. In addition, most series reporting a high percentage of patients with gall-bladders undergoing papillotomy are from European centers (see Table 4). So far, American physicians are apparently more inclined to refer such patients for cholecystectomy. A thorough search of Yale-New Haven Hospital records for the past two years (including reports from the radiology and gastroenterology departments, and hospital charts) revealed only twelve subjects suitable for this study (two of whom could not be reached). Many of these people are elderly and/or in relatively poor health (most were treated endo-scopically because of contraindications to surgery), making voluntary participation in a research study rather inconvenient. Taking this into consideration, it seems fortunate that six of the ten people contacted agreed to take part in the study. At any rate, the limited data obtained to this point raise several interesting questions, and allow preliminary conclusions as to the utility of cholescintigraphy in this population.

Cholescintigraphy after Endoscopic Papillotomy:

A major objective of this study was to determine if nonvisualization of the gallbladder by cholescintigraphy is a reliable indicator of cystic duct obstruction in post-papillotomy patients. In this series gallbladder nonvisualization occurred in three of six asymptomatic subjects who had undergone a previous endoscopic papillotomy. Although present data is limited, these results suggest a 50% false positive rate for cholescintigraphy in this population. This represents a dramatic reduction in specificity, and clearly undermines the utility of scintigraphy as a test for acute cholecystitis in patients with a prior endoscopic papillotomy. Using gallbladder nonvisualization as the sole diagnostic criteria, cholescintigraphy cannot distinguish acute cholecystitis from baseline conditions in perhaps half of these people. Of course, additional scintigraphic evidence of acute gallbladder disease may still be reliable in such patients, but such findings occur infrequently. These observations include: 1) the "rim sign" (increased pericholecystic activity) sometimes seen in gangrenous cholecystitis, gallbladder perforation, and severe gallbladder inflammation;[92,157-159] and 2) a photopenic mass effect in the gallbladder fossa, occasionally observed in cases of gallbladder distension resulting from empyema or emphysematous cholecystitis.[92]

The ability to ascertain the functional status of the cystic duct is extremely helpful in confirming or excluding a diagnosis of acute cholecystitis. Cholescintigraphy is the only imaging modality capable of assessing cystic duct patency. While sonography is an excellent means of detecting gallstones, the presence of stones does not prove the existence of acute cholecystitis.[92,94] In addition, many patients with an intact gallbladder after papillotomy have gallstones documented by prior studies. Using ultrasound to prove that the stones are still there is of questionable value. A negative ultrasound may prove helpful in demonstrating that prior stones have passed through the widened papillary orifice, but the clinical significance of finding stones on sonography is of limited usefulness in a patient with known gallstones. Ancillary sonographic findings (such as intramural sonolucency, pericholecystic fluid, sonographic Murphy's sign, gallbladder wall thickening, gallbladder distention, and sludge) may be helpful in diagnosing acute cholecystitis, but they are not always present, and are often non-specific.[92,94]

In summary, cholescintigraphy is the most appropriate diagnostic procedure in suspected cases of acute cholecystitis. It is therefore important to know if the results of scintigraphic scanning are as accurate in post-papillotomy patients as in the general population, especially since these individuals are potentially at high risk for both gallbladder disease and surgical complications.

Conclusions may be premature at this point, but the results of this small series suggest that cholescintigraphy is not a reliable test in this population. However, this study has also demonstrated that visualization of the gallbladder can occur in patients with a prior papillotomy (even in one case with radiographically documented incompetence of the sphincter of Oddi. Thus, a normal cholescintiscan in such a patient can exclude the possibility of acute cholecystitis, but a "positive" scan (i.e., nonvisualization of the gall-bladder) in a patient with an ablated sphincter of Oddi does not necessarily confirm this diagnosis.

Routine Baseline Cholescintigraphy:

In light of the apparently reduced accuracy of chole-scintigraphy in detecting acute cholecystitis following endoscopic papillotomy, it might prove useful to obtain baseline cholescintiscans in all individuals with an intact gallbladder after section of the sphincter of Oddi. This would provide diagnosticians with background results for comparison with future studies. In any person who demon-strates a normal baseline cholescintiscan following papil-lotomy, this imaging test can most likely be used with confidence to confirm or exclude the diagnosis of acute cholecystitis. However, in patients who do not show evidence of gallbladder filling after papillotomy, a subsequent "positive" cholescintiscan may in fact be related

to an incompetent sphincter of Oddi, as opposed to a blocked cystic duct. Baseline scintigraphy can therefore be employed to identify specific patients (i.e., those with gallbladder visualization) in whom subsequent cholescintigraphy would be of use should symptoms of acute gallbladder disease arise.

Since the number of patients with an intact gallbladder after papillotomy represents only a very small segment of the population, the overall cost of obtaining baseline scans in these people should not be prohibitive. Whether such information is clinically useful depends upon the frequency of acute cholecystitis in post-papillotomy patients. This rate has varied widely (from 0-25%) in different follow-up studies.[29,51-55,63,74,75,77,82,83] Combining the results of all these series gives an approximate 10% incidence of acute cholecystitis following endoscopic papillotomy. This risk is sufficiently high that obtaining routine post-papillotomy baseline scans may be warranted. Of course, baseline studies would only be useful if they provide reproducible results. It may be necessary to perform two or more scintiscans at set time intervals in a small group of subjects, in order to establish whether baseline findings remain stable.

If persons particularly at risk for acute gallbladder disease could be identified, then baseline scintigraphy might prove particularly helpful in this subgroup. So far, however, no clear predictors of future gallbladder disease have been determined. Investigators have looked at ERCP

findings and the presence of gallstones in this context,[56,80-83] but no studies have examined the possible value of scintigraphy as a predictor of long-term biliary complications. If nuclear imaging is routinely performed in post-papillotomy patients with an intact gallbladder, follow-up studies may eventually correlate long-term outcome with baseline cholescintigraphic findings. If this turns out to be the case, scintigraphy may be used to decide appropriate patient care after endoscopic papillotomy. Persons with a normal baseline scan may be managed simply by outpatient follow-up, while those demonstrating nonvisualization of the gallbladder may be referred for prophylactic elective cholecystectomy. Elective surgery involves significantly lower morbidity and mortality as compared to emergency operation,[14,17-19,22] and is certainly justified in patients at high risk for developing acute gallbladder disease in the future. The timing of scintigraphy following papillotomy is important. Early after transection of the sphincter, local edema may partially occlude the papilla, diminishing the size of the orifice. This temporary partial resistance to bile outflow may be sufficient to cause bile to enter the gallbladder. Baseline cholescintigraphy should be performed only after the incision has healed and early edema has subsided. The healing process should be complete by one month.

Possible Explanations for Gallbladder Visualization:

Despite prior endoscopic papillotomy, gallbladder filling occurred in three subjects in this study (50%), as demonstrated by scintigraphy. If contraction of the sphincter of Oddi is necessary for the gallbladder to fill, the observed normal cholescintiscans in these persons could have resulted from either: 1) residual contractility following only partial destruction of the sphincter by papillotomy; and/or 2) healing or restenosis of the sphincter. Endoscopic papillotomy does not necessarily result in total ablation of the sphincter of Oddi. This procedure is performed in order to treat a particular problem; such as choledocholithiasis, or symptoms attributed to papillary stenosis. Incomplete section of the sphincter may be sufficient to allow stone extraction and/or relieve a person's symptoms. Thus, following papillotomy, some patients might be left with a partially ablated (as opposed to a completely non-functional) sphincter of Oddi. In such cases, the remaining sphincteric activity may be adequate to at least partly occlude the common bile duct, thereby diverting bile into the gallbladder and preventing reflux of air or contrast into the biliary tract.

Endoscopic manometry of the biliary tree is the definitive method of assessing sphincter of Oddi physio-logy.[137,138,160] This technique has been widely used to evaluate patients with persistent abdominal pain following

cholecystectomy, the so-called "post-cholecystectomy syndrome."[6,161-167] The results of manometric studies suggest that anatomic and/or functional disorders of the sphincter of Oddi may be responsible for such symptoms in some of these individuals. A plethora of terms (such as papillary stenosis, ampullary stenosis, stenosing papillitis, fibrotic Odditis, spastic sphincter of Oddi, hypertonic Oddi´s sphincter dyskinesia, biliary dyskinesia, and others) have been used to describe these entities, which can be collectively referred to as sphincter of Oddi dysfunction.[165,166] Findings of elevated basal pressures in the common duct and region of the sphincter of Oddi, as well as an elevated common duct-to-duodenum pressure gradient, provide objective evidence of sphincter stenosis or dysmotility.[6,161-167]

Several investigators have used endoscopic manometry to examine the effect of surgical sphincteroplasty and endoscopic papillotomy on biliary pressures.[161-163,167-173] All of these studies reported a striking reduction in mean basal sphincter of Oddi pressure and common duct-to-duodenum pressure gradient following endoscopic papillotomy. Although biliary manometry represents the current "gold standard" for evaluating the presence or absence of sphincter activity, it is an invasive procedure that is not widely available. As an alternative, non-invasive imaging methods have often been used to verify incompetence of the sphincter of Oddi.[12,52,56,70,78,135,153,163] These include: 1) examina-

tion of plain abdominal films for the presence of air in the biliary tree, and 2) upper GI studies to demonstrate reflux of contrast material from the duodenum into the common bile duct. Escourrou et al.[52] performed abdominal radiography and barium studies in 60 post-papillotomy patients. They noted biliary air in 70% of persons and common duct reflux in 65% of patients. Cotton observed these radiographic findings in "about two thirds of patients" following papillotomy.[56] Winstanley et al.[78] noted bile duct gas on plain film in 14 (41%) of 34 patients at long-term (18 months to five years) follow-up examination. They also noted air on ultrasound in ten individuals, although only five of them had evidence of biliary air on plain film. The authors concluded that "Although gas was observed in only 41% of cases, it may have been present and undetected in many more, as suggested by the results of the ultrasound examinations."

This investigation employed all of these radiologic methods (plain film, sonography, and limited upper GI examination) to assess the status of the sphincter of Oddi. Imaging studies revealed evidence of an incompetent sphincter in only three (50%) of six subjects. The meaning of these findings is unclear, however, because the sensitivity of these imaging techniques in detecting sphincter incompetence has never been determined. In one study,[163] eight patients with radiographic evidence of biliary air after endoscopic papillotomy were tested with manometry. All eight persons had basal sphincter pressures of 0 mm Hg.

These results suggest that (in the absence of biliary-enteric fistulae) the finding of air in the biliary tree is highly specific for a non-functional sphincter of Oddi. However, no conclusions regarding the sensitivity of this finding can be drawn from this small series, since post-papillotomy manometry was not performed on patients in whom biliary air was not seen. Thus, while the presence of air or contrast reflux are highly suggestive of an incompetent sphincter of Oddi, the inverse may not be true. Lack of these findings does not necessarily prove that the sphincter is functioning normally.

Investigators have also studied the possible occurrence of healing and restenosis of the sphincter of Oddi after endoscopic papillotomy. Geenen et al.[173] measured the change in size of papillotomy incisions at twelve and 24 month follow-up examinations. They noted a slight decrease in incision length (from a mean of 11.6 mm to 8.3 mm) in 22 patients after one year, and a lower reduction in size (from a mean of 7.5 mm to 6.5 mm) in eight persons between one and two years after papillotomy. Follow-up manometry documented dramatically diminished basal sphincter of Oddi pressure and common duct-to-duodenal pressure gradient (as compared to pre-papillotomy values), in all subjects. The authors obtained consistent and reliable estimates of papillotomy incision length by 1) gauging the size of the orifice in reference to the diameter of the papillotome catheter, and 2) passing balloon catheters inflated to a known diameter

through the papillary opening. This study suggests that, although some healing of the incision takes place over time, endoscopic papillotomy likely results in a substantial disruption of sphincter of Oddi contractility for at least two years.

Restenosis of the sphincter of Oddi has been described after endoscopic papillotomy, but this occurs very rarely, with a reported incidence of 0.9-4.3%.[36,41,75,77] Of note, one follow-up study found a greater incidence (2 [8.3%] of 24 patients) of restenosis in persons treated endoscopically for sphincter of Oddi stenosis, as compared to those with common duct stones (10 [2.3%] of 438 patients).[77] Of the three subjects in this study with no radiologic evidence of sphincter incompetence, one (subject #3) had been treated for presumed spasm of the sphincter, one (subject #4) for sphincter stenosis, and one (subject #5) for common duct stones. Despite complete relief of symptoms in all three subjects, restenosis of the papilla may have occurred, and this could account for the observed gallbladder filling in these individuals.

Hospital records of the subjects in this study were reviewed to determine the estimated size of the papillotomy. Not surprisingly, this variable did not correlate with cholescintigraphic findings in this small series (see Table 8). For example, the gallbladder visualized in subject #4 despite a 1.5 cm incision, while no gallbladder filling occurred in subject #5, following a 1 cm papillotomy.

Incision size, however, is not a reliable indicator of the degree of sphincter ablation. The length of the choledochal sphincter in man varies greatly from individual to individual.[12,174] Thus, while a small cut may totally sever the muscle in one person, another patient may retain some sphincter activity after a relatively large incision. Furthermore, in this series, papillotomy incision size was estimated visually, without the use of objective measuring techniques. Since all papillotomies were performed by the same endoscopist, these estimates are probably consistent, but the lack of objective data precludes drawing any conclusions based on incision length.

Since papillotomy incision size has been shown to decrease over time,[173] hospital records of the subjects in this study were reviewed to ascertain the time since papillotomy. This interval ranged from one to 21 months. No correlation of either scintigraphic or radiographic findings and post-papillotomy follow-up period was noted (see Table 8), allowing no conclusions regarding the potential effects of sphincter healing on biliary physiology.

The final variable measured in this study was the clinical outcome following endoscopic papillotomy. This also did not correlate with radiographic or scintigraphic findings. All subjects in this series claimed to have remained free of symptoms since papillotomy. Clinical improvement, however, provides very weak evidence of sphincter ablation, since this can be attributed to: 1)

partial loss of sphincter function, or 2) a placebo effect of interventional therapy.[175] A placebo effect has been seen in patients treated with sham papillotomy in a randomized trial.[167]

Possible Explanations for Gallbladder Nonvisualization:

Gallbladder filling was not seen in three subjects in this study (50%). Besides the papillotomy, other factors which could account for a lack of gallbladder visualization include: 1) asymptomatic cystic duct obstruction, 2) chronic cholecystitis, and/or 3) a disorder of gallbladder motility. These conditions may have been present in two of these three subjects. Other reported causes of false positive cholescintigraphy (alcoholism, pancreatitis, severe intercurrent illness, hyperalimentation, prolonged fasting, and trauma)[92] were present in none of these subjects.

Cystic duct obstruction is possible in subject #2. On her initial ERCP the cystic duct and gallbladder did not opacify. Multiple abdominal radiographs taken during her period of hospitalization demonstrated one or more calcified gallstones in the region of the cystic duct and gallbladder neck. On her second ERCP, the cystic duct filled with contrast (see Figure 14B). The gallbladder was not seen, but no attempt was made to visualize it, once filling of the cystic duct became apparent. Although unlikely, occlusion at the neck of the gallbladder cannot be ruled out, since a

fully patent biliary tract has never been radiographically documented in this subject. However, one can also raise several arguments against cystic duct obstruction in this subject. First of all, it has already been stated that a lack of gallbladder filling on ERCP does not prove that the cystic duct is blocked.[85] Bile stasis related to common duct obstruction can apparently produce the same finding. Secondly, serial abdominal films documented that the subject passed several stones from the gallbladder after papillotomy. Upon discharge, plain film revealed three calcified stones in the fundus of the gallbladder. On the day of the study only one gallstone was evident on plain film, and no stones were seen in the area of the cystic duct. Obviously, stones cannot leave the gallbladder if the cystic duct is occluded! In summary, the cystic duct must have been patent on at least several occasions in subject #2. The existence of a blocked cystic duct on the day of the study is unlikely, but this possibility cannot be ruled out.

As described previously, chronic cholecystitis is a recognized cause of false positive cholescintiscans.[92,94] Both subjects with nonvisualized gallbladders demonstrated abnormal sonographic findings which have been associated with chronic cholecystitis. Subject #2 had a small gallbladder and cholelithiasis, a common sonographic appearance of chronic cholecystitis.[92,94] Subject #5 had a thickened gallbladder wall, measuring 6 mm (normal 2 mm or less[92]). The significance of this sonographic finding is unclear;

gallbladder wall thickening has been seen in several condi-
tions, including acute and chronic cholecystitis, ascites,
and gallbladder contraction following a meal[92,176,177]
(subject #5 consumed a bowl of instant oatmeal four hours
prior to her ultrasound examination). The presence of gall-
stones places both of these subjects at risk for chronic
cholecystitis. However, both subjects claimed to be free of
symptoms of biliary disease since papillotomy.

Studies have suggested that cholelithiasis is often
associated with gallbladder dysmotility. One quantitative
scintigraphic study noted diminished gallbladder filling in
patients with gallstones as compared to controls.[178] A later
study, however, did not confirm this observation, but did
demonstrate a decrease in mean gallbladder ejection fraction
in patients with gallstones.[179] One cannot attribute gall-
bladder nonvisualization purely to the presence of gall-
stones, since cholescintigraphy will visualize the gall-
bladder in most patients with cholelithiasis. Indeed, if the
mere existence of gallstones prevented gallbladder visual-
ization, then scintigraphy would be no more useful than
sonography in confirming a diagnosis of acute cholecystitis.
Scintigraphic abnormalities seen in patients with chole-
lithiasis must therefore be due to associated gallbladder
dysfunction. In a recent study, Spengler et al.[180] employed
ultrasonography to measure parameters of gallbladder
contraction (residual volume and ejection half-time, in
response to CCK administration) in patients both before and

after gallstone fragmentation by extracorporeal shock-wave lithotripsy (ESWL). They found evidence of diminished gallbladder motility in persons with gallstones as compared to controls, which remained unchanged one year after stone destruction by ESWL. Possible explanations for this observation include: 1) cholelithiasis causes a permanent disorder of gallbladder motility, 2) gallbladder dysmotility precedes and predisposes to stone formation, or 3) these two conditions share a common etiology.

Another potential cause of gallbladder dysmotility is the autonomic neuropathy often seen in diabetes mellitus. Clinical studies have afforded evidence of impaired gallbladder function in diabetics.[181,182] As compared to non-diabetic controls, decreased gallbladder contraction following meals has been seen in female diabetic patients, even more commonly among those with diabetic autonomic neuropathy and retinopathy.[181] Two of the three subjects whose gallbladder failed to visualize on scintigraphy are diabetics (#2 and #5, both females). According to subject #2´s personal physician, she suffers from peripheral neuropathy, but has no symptoms of autonomic dysfunction. The possibility of a diabetic-induced biliary neuropathy contributing to gallbladder nonvisualization must be considered. Finally, if diabetic neuropathy can lead to functional denervation of the gallbladder, perhaps denervation of the sphincter of Oddi might also occur in some patients. This has not been described. No study has

evaluated baseline cholescintigraphic findings in diabetics.

The potential presence of a chronically diseased gallbladder and/or disordered biliary motility, as well as the possibility of asymptomatic cystic duct obstruction, represent confounding variables which interfere with the interpretation of the data obtained in two subjects. Lack of gallbladder visualization on cholescintiscan cannot be attributed purely to a lack of sphincter of Oddi contraction, especially in a study with such a small experimental group. In fact, one of these two subjects (#5) had no radiographic evidence of sphincter incompetence. Although this subject's gallbladder was seen on a prior cholescintiscan in 1981, much could have occurred (such as progression of a biliary motility disorder) in the intervening eight years to account for the currently observed lack of gallbladder filling. Unfortunately, a cholescintiscan performed one month before her papillotomy showed complete extrahepatic obstruction, with no excretion of tracer from the liver at four hours post-injection, rendering assessment of the gallbladder and cystic duct impossible. In summary, the significance of these additional factors can only be resolved by statistical analysis of results from a larger study group.

The Role of the Sphincter of Oddi in Gallbladder Filling:

A second objective of this investigation was to acquire
further evidence regarding the importance of a functional
sphincter of Oddi in the process of gallbladder filling in
humans. Unfortunately, data on this topic are contradictory.
The results of studies in subject #1 clearly demonstrate
that gallbladder filling can occur even in the setting of a
non-functional sphincter of Oddi. Sphincter incompetence in
this subject was strongly suggested by the finding of
biliary air on both plain abdominal film and ultrasono-
graphy, and the demonstration of contrast reflux from the
duodenum into the common bile duct, followed by rapid
drainage of barium. These findings thus suggest that gall-
bladder filling may depend upon other physiologic
mechanisms, in addition to any role played by sphincter of
Oddi contraction. However, in subject #6 nonvisualization of
the gallbladder most likely occurred as a result of the loss
of sphincter activity following endoscopic papillotomy,
since the gallbladder was seen on a prior cholescintiscan
done two days before the procedure. Studies in subject #6
also showed evidence of sphincter incompetence (biliary air
on both plain film and ultrasound). Findings in this subject
thus imply a crucial role of the sphincter of Oddi in gall-
bladder filling. These contrasting results can only be
resolved by collecting additional data.

As described in the introduction, experimental data on the control of gallbladder filling are extremely variable (see Table 7 for an overall summary). While some studies clearly illustrate the importance of a passive filling mechanism, others suggest the possibility of an active role played by the gallbladder (perhaps in conjunction with the spiral valves of the cystic duct). Some of the contradictory results may be related to differences among the species studied. Biliary physiology probably varies in different animals. As previously mentioned, experiments in cats[131] and rabbits[152] suggest that a functional sphincter of Oddi is necessary for the gallbladder to fill. Studies in dogs,[86,87,132-134,150,152] however, question the import of the sphincter in this process, with many investigators invoking contraction of the surrounding duodenal musculature as the force responsible for passive gallbladder filling.[132-134,150] The study by Tansy et al.[152] clearly demonstrated the importance of the terminal common bile duct in gallbladder filling in dogs, but showed that neither action of the sphincter nor the duodenal musculature was responsible for this effect. The actual force controlling the flow of bile into the gallbladder is not known. Contradictory results have also been found in humans, but these may be technique related. Jones and Smith[70] noted non-visualization of the gallbladder on oral cholecystography in patients following sphincteroplasty, while Lempke[135] observed normal gallbladder filling after sphincterotomy.

This variability may have resulted from the existence of residual sphincteric activity. Sphincteroplasty usually produces total ablation of the sphincter of Oddi, while surgical sphincterotomy leaves part of the muscle intact.[12]

Considering the results of numerous studies, as well as the observations in this investigation, it seems likely that gallbladder filling depends upon multiple physiologic factors. If so, a complete lack of gallbladder filling (as evidenced by nonvisualization of the gallbladder on chole- scintigraphy) may only occur in patients in whom all normal regulators of bile flow have been disrupted. As stated previously, gallbladder nonvisualization among the subjects in this study may not be related solely to a lack of sphincter activity, but rather to the combined effect of an ablated sphincter and an abnormal gallbladder. Two subjects in this study (#3 and #4) have never had documented gall- stones, but had endoscopic papillotomy performed because of sphincter of Oddi stenosis or spasm. The gallbladder filled in both of these subjects. It is possible that, in persons with normal gallbladder motility, the hypothetical active component of the filling process may alone be sufficient to fill the gallbladder, regardless of the functional integrity of the sphincter. Unfortunately, conclusions regarding the importance of sphincter activity in gallbladder filling in these two subjects may be unjustified, since neither had radiographic evidence of a patent papillotomy.

In order to truly ascertain the role of the sphincter of Oddi in gallbladder filling, an experimental model would have to hold other potential variables constant. In other words, determination of the relative contribution of sphincter activity to this process may require performing this study in persons with an otherwise normal biliary system. Of course, such a study would be impossible in humans, since endoscopists (hopefully) do not perform papillotomies on patients with a normal biliary system! However, it may be interesting to compare post-papillotomy scintigraphic findings in patients treated for sphincter of Oddi stenosis or spasm versus those treated for stone disease. This study included subjects from both of these groups, but the present numbers are insufficient to draw conclusions. Perhaps patients with isolated disorders of the sphincter of Oddi are more likely to have normal gallbladder function. It is unfortunate that this study did not employ a scintigraphic technique for measuring gallbladder ejection fraction,[86,183] which would have assessed gallbladder motility in these subjects. This is an interesting prospect for future research. In persons whose gallbladder does not visualize on scintigraphy, gallbladder ejection fraction may be estimated by calculating gallbladder volume sonographically both before and after administration of CCK.[184]

Despite the small number of subjects, this study has clearly shown that gallbladder filling can occur in a patient in the presence of radiographically documented

sphincter incompetence. Thus, the sphincter of Oddi may not function as the sole regulator of bile flow into the gall-bladder. This information alone cannot determine whether the gallbladder fills by an active or passive mechanism. If occlusion of the terminal common bile duct is required for the gallbladder to fill, other physiological events, including constriction of the surrounding duodenal muscula-ture, or the action of some presently unknown mechanism (such as the "vascular dynamics of the ductal epithelium" proposed by Tansy[152]), may fulfill this purpose in persons lacking a functional sphincter of Oddi. Gall-bladder filling is probably influenced by several physiologic factors, including sphincter contraction, duodenal contraction, gallbladder motility, and possibly others. Elimination of only one of these variables may not result in a measurable physiologic effect. However, simultaneous interference with two or more potential controlling mechanisms may allow determination of the various forces responsible for gallbladder filling. It would be interesting to repeat this study in subjects with endo-scopically placed internal biliary stents.[185-189] This would effectively eliminate any occlusive effect of both the sphincter and the duodenal musculature on the common bile duct. The occurrence of scintigraphic gallbladder visualization in subjects with biliary endoprostheses would provide a strong argument for an active filling process (provided it could be shown that the stent itself does not occlude the cystic duct).

Confounding factors may be present, however, since many patients receive these prosthetic devices for relief of malignant biliary obstruction. In such cases, the underlying disease may affect bile flow in the ducts and gallbladder. Stents are also used to maintain biliary drainage when stones cannot be removed[186,189] (this was done in subject #2). Such persons are probably more suitable candidates for studies of bile flow.

Hepatic Excretion of Radiopharmaceutical:

An unexpected result of this study was the finding that five (83%) of six subjects demonstrated delayed hepatic excretion of radioisotope. This observation is in direct opposition to the expected results. In designing this study, it was assumed that most of the subjects would demonstrate unusually rapid clearance of tracer from the liver, due to the decreased resistance to bile flow out of the common duct. In patients with either common duct stones or papillary stenosis, isotope washout rates from the liver have been seen to increase in nearly all patients following papillotomy[190,191] and after surgical biliary drainage.[192] This observation was noted in only one subject in this study (#2, see Figure 17B). It is not clear why excretion was delayed in the remaining five subjects.

Quantitative cholescintigraphy has been shown to be highly sensitive in detecting derangements in hepatic

function. Abnormal liver uptake and clearance has been seen in various types of hepatobiliary disease, including acute viral hepatitis, intrahepatic cholestasis, and extrahepatic obstruction.[191,192] Scintigraphic evidence of liver dysfunction has also been observed in patients with normal serum liver function tests.[191] This is precisely the situation seen in subjects #3 and #6. Liver function tests were not done as part of the experimental protocol, and thus were not available in the remaining four subjects. Although patients with intra- and extrahepatic cholestasis have shown an improvement in scintigraphically measured liver function following resolution of disease, quantitative indices do not always return to normal range.[191,192] This might explain the observed derangements in hepatic function seen in five subjects. It is also possible that sphincter ablation somehow leads to impaired hepatic excretion. This has never been described, but the few studies on post-papillotomy scintigraphy have nearly exclusively involved patients with prior cholecystectomy. Perhaps the combined presence of a gallbladder and an ablated sphincter produces some as yet unknown detrimental effect on liver function.

Finally, in using excretion curves to ascertain papillotomy patency, one must realize that measurement of hepatic clearance is only an indirect method of assessing flow resistance in the common duct. Delayed excretion of tracer from the liver may mask rapid drainage from the common bile duct. In the absence of extrahepatic obstruc-

tion, liver excretion may be the rate-limiting step in bile flow. Thus, even a widely gaping papillary orifice will not accelerate isotope clearance from a dysfunctional liver. A true measurement of the physiologic effect of a papillotomy would require quantification of clearance of tracer from the common bile duct. Although some researchers have encountered difficulty in distinguishing bile duct activity from that of the surrounding liver parenchyma,[191] others have been able to quantify ductal bile flow by outlining regions of interest (ROI) over the common hepatic and common bile ducts.[154,179,193] However, since labelled bile must pass through the liver before entering the ductal system, impairments of hepatic function would also interfere with flow measurements in the bile ducts. A widely patent papilla may allow tracer to pass rapidly from the common duct into the duodenum, but this effect might be concealed by the prolonged period of entry into the duct from a diseased liver.

The ability to discern rapid bile flow out of the common duct regardless of hepatic function would require a quantitative technique which either corrects for, or is independent of, abnormalities in the hepatic excretion rate. Stritzke et al.[193] have described a computer algorithm based on substraction of background liver activity, which they have used to determine the time of appearance of tracer in the common duct in cases of biliary obstruction. It is not known whether they have used this method to assess duct

clearance after papillotomy. As an outgrowth of this research, a rapid frame "cine IDA scan" was developed (serial 1 minute images displayed in motion picture form), which can follow the flow of tracer down the common duct. This method is presently being evaluated as a means of measuring bile duct flow in normal individuals and those with known liver disease. A third possibility would involve determination of typical clearance parameters in regions of interest over the liver and common duct, in both normal individuals and persons with liver disease. This method should be able to illustrate whether altered hepatic excretion affects the measured washout of tracer from the duct, and may also generate a reliable correction factor for adjusting calculated common duct clearance in the presence of abnormal liver excretion. If either of these techniques proved successful, scintigraphy could offer a simple non-invasive method for estimating the adequacy of a papil-lotomy. As described, endoscopic biliary manometry is the current "gold standard" for evaluating sphincter of Oddi activity. As compared to an endoscopic procedure, a nuclear hepatobiliary scan is much more tolerable to patients, and less costly. Thus, assessment of biliary function after sphincter ablation might represent a useful application of quantitative cholescintigraphy.

Future Plans:

This investigation will continue. As additional patients with an intact gallbladder undergo endoscopic papillotomy, they will be invited to participate as research subjects. It may also be helpful to expand this study to include multiple centers, thus providing a larger population from which to draw subjects. With a sufficiently large sample size, the influence of confounding variables should be minimized, and a definitive answer to the question of gallbladder filling in persons after papillotomy may be obtainable. Furthermore, including the following studies in the experimental protocol may yield additional useful information: 1) measurement of gallbladder motility (ejection fraction in response to CCK), 2) quantification of tracer flow within a region of interest over the common bile duct (to directly assess drainage through the papillotomy), 3) measurement of pre- and post-papillotomy fasting gallbladder volume by ultrasonography.

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